Invasive and non-invasive indices of myocardial ischemia

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MYOCARDIAL ISCHAEMIA: A COMPARISON OF INVASIVE AND NON-INVASIVE INDICES

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ABSTRACT

Recent guidelines for the management of stable coronary artery disease (CAD) and myocardial revascularisation emphasise the importance of the presence of ischaemia for guiding revascularisation. Cardiovascular Magnetic Resonance (CMR) perfusion imaging and fractional flow reserve (FFR) are two methods of physiological ischaemia assessment, one invasive and the other non-invasive.

In order that the results are interpreted accurately, it is important to be aware of the limitations and advantages of each technique. These techniques measure different parameters so it is not uncommon that the two tests may lead to differing results in one patient. In addition, the extent and not just the presence of ischaemia are increasingly considered to be an important variable that needs to be considered.

The aim of this thesis is to assess the similarities and differences in ischaemia assessment between the two tests, in particular in the assessment of ischaemic burden and also on specific clinical scenarios such as microvascular and multivessel disease.

Firstly, a close correlation between the extent of ischaemia measured by CMR and the FFR value itself is demonstrated. FFR measurement has previously been used as an indicator of the presence of ischaemia alone and the relationship with ischaemic extent has never been proven. It is an interesting finding, which lends weight to the strategy of targeted revascularisation aiming for the greatest reduction in ischaemic burden. The FFR value itself as an indicator of ischaemic burden is also useful in centres that do not have access to sophisticated imaging techniques such as CMR.

Secondly, another simple method of invasive estimation of ischaemic burden is demonstrated via the use of a functional jeopardy score. This is validated against CMR but is limited by a tendency to overestimate the extent of ischaemia. The use of the FFR value itself, as demonstrated in chapter 4, therefore offers better potential as a marker of ischaemic extent.

Two examples of areas where there may be discrepant results are in patients with multivessel disease and patients with microvascular disease. A comparative analysis of the

diagnostic accuracy of these two tests in multivessel disease demonstrates reasonable concordance but does lead us to question which test is the diagnostic reference standard. In the discrepant cases, it is unclear whether CMR underestimates or FFR overestimates the number of perfusion territories.

Finally, a novel method of non invasively differentiating between multivessel disease and microvascular disease is demonstrated, providing a feasible solution to this diagnostic dilemma. Multivessel CAD and microvascular disease can be accurately distinguished using the novel concept of perfusion dephasing analysis, which analyses the spatio-temporal variability in the distribution of myocardial perfusion to the LV myocardium. An improved diagnostic algorithm of CMR is therefore proposed, including the analysis of the variance of time to peak signal intensity, the most accurate index for perfusion dephasing. This has the potential for patient benefit in the reduction of unnecessary invasive angiography procedures.

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DECLARATION

The work in this thesis is my own. I helped with the design of the MR- INFORM study, wrote the protocol, ensured that the ethics committee and R and D departments approved the study, and proceeded to set up the study as a multicentre study. I recruited and scanned the patients that were recruited in my centre. I analysed all the CMR scans that were included in my studies, interpreted the data, carried out the statistics and wrote the script. I collaborated with Dr Amedeo Chiribiri for the work presented in chapter 6. We designed the study together; I helped to recruit the patients, helped with collation of the data and contributed to the data analysis. Dr Chiribiri has given permission for this data to be presented in this thesis.

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ABBREVIATIONS

AHA - American Heart Association

ACE I - angiotensin converting enzyme Inhibitor

APPROACH - Alberta provincial project for Outcome Assessment in Coronary Heart Disease Score

AUC - area under the curve

BARI - bypass angioplasty revascularisation Index

CAD - coronary artery disease

CABG - coronary artery bypass grafting

CCS - Canadian class symptoms

CFR - coronary flow reserve

CMR - cardiovascular magnetic resonance

CTO - chronic total occlusion

CX - circumflex artery

ESC - European Society of Cardiology

FFR - fractional flow reserve

FP - false positive

FN - false negative

HR - heart rate

LV - left ventricle

LGE - late gadolinium enhancement

LAD - left anterior descending artery

NPV - negative predictive value

OM - obtuse marginal branch

PPV - positive predictive value

PCI - Percutaneous Intervention

SBP - systolic blood pressure

SD - standard deviation

SPECT- single photon emission computed tomography

TP – true positive

TN – true negative

RCA – right coronary artery

MACCE - major adverse cardiac and cerebrovascular events

MCE - myocardial contrast echocardiography

MI - myocardial infarction

MPR - myocardial perfusion reserve

MBF – myocardial blood flow

RPP- rate pressure product

QCA - quantitative coronary angiography

THESIS OVERVIEW

Myocardial ischaemia as a consequence of coronary artery disease (CAD) is a major cause of mortality and morbidity.

There are many different methods of ischaemia assessment, which are the subject of intense research with the aim of improving assessment and guiding therapy. Recently, the use of ischaemic burden to target revascularisation is gaining interest as a therapeutic goal with the aim of providing prognostic benefit for the patient.

Cardiovascular Magnetic Resonance (CMR) perfusion imaging is increasingly used as a method of ischaemia assessment due to its high diagnostic accuracy and potential for the measurement of ischaemic burden. However, not all centres have access to CMR perfusion imaging whilst most interventional practices increasingly use fractional flow reserve (FFR) for the assessment of ischaemia.

This thesis seeks to further our understanding of the differences between CMR and FFR in the assessment of ischaemia and ischaemic burden and, in particular, the areas of discordance between the two methods. The ability to understand these differences allows the more appropriate selection of assessment method thus bringing us closer to our goal of improved patient care.

The first part of this thesis focuses on the assessment of ischaemic burden. The second part concentrates on the areas of discrepancy between the two tests with a particular focus on microvascular and multivessel disease.

Chapter 1 In the first chapter I review the evidence for the use of CMR and FFR for the physiological assessment of ischaemia. In particular I focus on the importance of using ischaemia and ischaemic burden to guide revascularisation.

Chapter 2 In this chapter, I describe the potential areas of discrepancy between the two diagnostic modalities. An understanding of these is vital for the appropriate interpretation of test results and subsequent decision making for the patient.

Chapter 3 Describes the concept, design, and the rationale behind the MR-INFORM trial. This is a randomised-controlled trial comparing stress perfusion CMR with FFR to guide the management of patients with stable coronary artery disease.

Chapter 4 In this chapter, I examine the correlation between FFR value and the extent of ischaemia measured by CMR. Although the FFR value provides a measure of the physiological significance of a stenosis, its relationship with ischaemic burden has never previously been described.

Chapter 5 Describes the validation by CMR of an invasive method of measuring ischaemic burden. In this chapter a novel "functional jeopardy score " is described and tested. This is particularly useful in centres, which do not have access to a non-invasive perfusion service.

Chapter 6 Compares areas of discordance in patients with multivessel disease. It is recognised that there is a potential for discrepancy between invasive and non-invasive assessment of ischaemia in patients with multi-vessel disease. A comparison between CMR and FFR in this complex group of patients has never previously been done.

Chapter 7 Focuses on a new method of differentiation between microvascular and multivessel disease by using dephasing analysis. A common diagnostic dilemma is the interpretation of widespread circumferential ischaemia, with patients with microvascular disease quite often being referred for angiography to rule out significant coronary disease.

Any technique that allows differentiation of these two different pathological entities will potentially affect patient management.

Chapter 8 Summarises the findings of this work and gives an outlook on future projects.

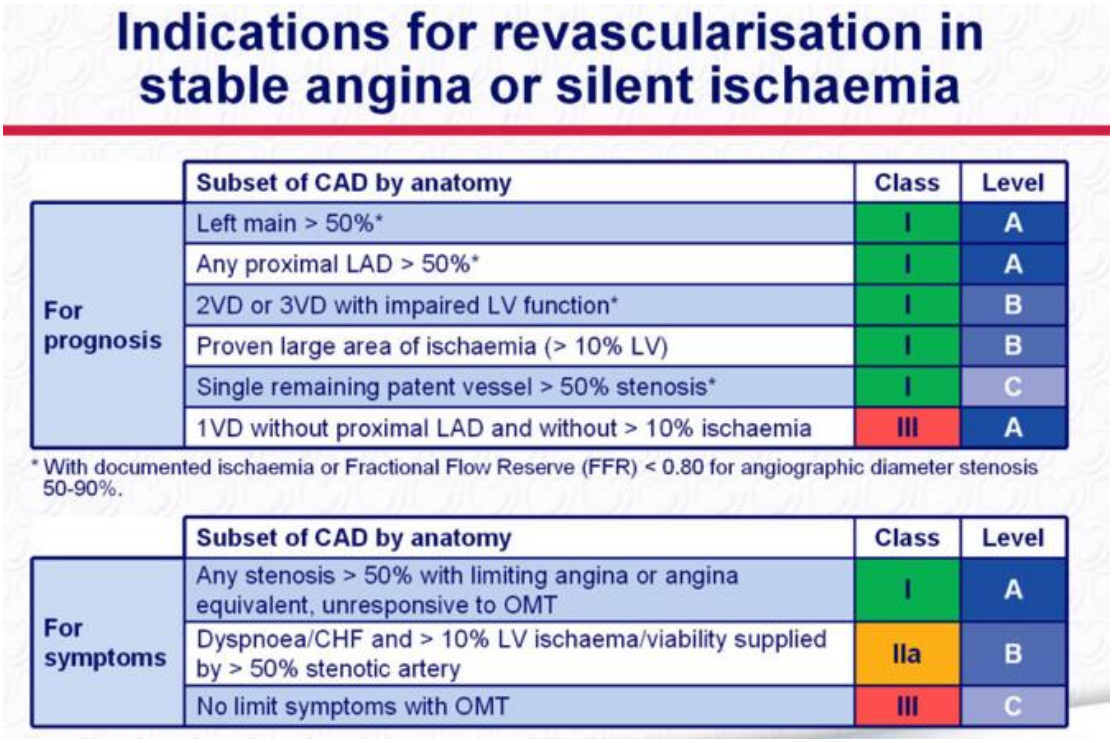
CHAPTER 1: INTRODUCTION

Coronary artery disease (CAD) remains a major cause of death and disability around the world. In patients with CAD, the accurate diagnosis and assessment of myocardial ischaemia is essential both for diagnostic and treatment purposes. Functional information on the significance of a coronary artery stenosis is increasingly used to decide on the management of patients with coronary artery disease (1). The importance of physiological lesion assessment has been acknowledged by the latest European Society of Cardiology (ESC) guidelines on myocardial revascularisation (2) (see Fig 1.1), which recommend that physiological assessment occur before consideration for revascularisation, especially for intermediate lesions. Revascularisation of lesions without functional significance can then be deferred if required. The European guidelines(2) have suggested the implementation of a multi-disciplinary heart team consisting of an imaging specialist, an interventionist, and a cardiac surgeon with the documentation of ischaemia using non-invasive imaging prior to making a decision. Additionally, the guidelines also highlight the importance not only on the presence of ischaemia, but also the extent of ischaemia i.e. ischaemic burden to be used to guide decision-making.

Non-invasive imaging modalities that incorporate ischaemia assessment include perfusion imaging by single photon emission computed tomography (SPECT), stress echocardiography and cardiovascular magnetic resonance (CMR) perfusion imaging. CMR perfusion imaging is a relative newcomer in the arena of diagnostic imaging. While most literature on non-invasive assessment of ischaemia is based on SPECT, CMR has shown advantages such as higher spatial resolution (3, 4) and potentially better diagnostic accuracy (5) whilst avoiding the use of ionising radiation.

Fractional Flow Reserve (FFR) is an invasive assessment of haemodynamically significant stenosis that is used in the catheterisation laboratory to guide revascularisation. The ESC guidelines(2) recommend FFR guided percutaneous intervention (PCI) when objective evidence of vessel related ischaemia has not been established prior to catheterisation. Whilst FFR is convenient and relatively easy to use, it gives an indication of the presence of ischaemia only, without any indication of its extent.

The ESC guidelines(2) also recommend that the heart team should agree on the indication for myocardial revascularisation. This includes documented ischaemia or FFR <0.80 for all lesions between 50- 90% or >10% ischaemia (see Fig 1.1)



Indications for revascularisation in stable angina or silent ischaemia

	Subset of CAD by anatomy	Class	Level
For prognosis	Left main > 50%*	I	A
	Any proximal LAD > 50%*	I	A
	2VD or 3VD with impaired LV function*	I	B
	Proven large area of ischaemia (> 10% LV)	I	B
	Single remaining patent vessel > 50% stenosis*	I	C
	1VD without proximal LAD and without > 10% ischaemia	III	A

* With documented ischaemia or Fractional Flow Reserve (FFR) < 0.80 for angiographic diameter stenosis 50-90%.

	Subset of CAD by anatomy	Class	Level
For symptoms	Any stenosis > 50% with limiting angina or angina equivalent, unresponsive to OMT	I	A
	Dyspnoea/CHF and > 10% LV ischaema/viability supplied by > 50% stenotic artery	IIa	B
	No limit symptoms with OMT	III	C

Fig 1.1: European Society of Cardiology guidelines on myocardial revascularisation. (Adapted from (2))

While there is a significant body of literature on the accuracy of both CMR and FFR for the detection of CAD, there are limited data on their comparability in the assessment of different clinical scenarios such as multivessel disease and microvascular disease..

There are important differences in the two techniques that need to be understood in order to appreciate the strengths and limitations of each technique.

1.1 Overview of CMR perfusion imaging

CMR itself has advantages over other forms of non-invasive imaging in that it allows a comprehensive examination of the heart including structure, function, perfusion and scar.

This is done without the use of ionising radiation and with sufficiently high resolution to delineate transmural differences of myocardial blood flow and scar.

First pass myocardial perfusion imaging involves achieving maximal coronary vasodilatation, usually with intravenous adenosine, and imaging the first passage of a contrast bolus into the myocardium. Perfusion of contrast into the myocardium subtended by vessels with flow limiting CAD does not increase with stress as much as in myocardium supplied by normal vessels. In the clinical setting, this is analysed qualitatively as a defect in the contrast perfusion into the myocardial wall visible with stress but not at rest.

In addition, semi- quantitative analyses such as the upslope of the myocardial time intensity curves have been used. Fully quantitative analysis allows the absolute quantification of myocardial blood flow (MBF) through the use of complex mathematical modelling. These techniques, however, remain within the research arena and are rarely used for clinical decision-making.

1.1.1 CMR VALIDATION STUDIES

Validation of CMR myocardial perfusion imaging has been performed in both animal and clinical studies. Initially important animal model studies(6) proved CMR superiority over SPECT for the identification of haemodynamically significant CAD. In a study by Lee et al (6), instrumented dogs had the circumflex artery partially occluded. Regional differences in flow, quantified using microspheres, were compared with CMR and SPECT imaging. The high spatial resolution of CMR enabled transmural flow to be evaluated in 3 to 5 layers across the myocardial wall. Reductions in subendocardial flow were visually apparent in CMR images. Endocardial-to-epicardial gradients in CMR flow increased progressively with stenosis severity, whereas transmural flow patterns in remote normally perfused myocardium remained normal. Flow reductions of <50% not identified by radionuclide imaging were apparent in CMR. See Fig 1.2

Additionally absolute quantification of myocardial blood flow by CMR perfusion is well validated against microspheres(7, 8). In a study by Christian et al(7), coronary artery occlusion was successfully performed in 16 animals. Fully quantitative (i.e. absolute) analysis

of myocardial blood flow (MBF) at CMR imaging correlated with microsphere MBF measurement (r = 0.95, P < .001) across the full range of blood flow rates encountered (from 0 to >5.0 mL/min/g). Furthermore, close correlations were demonstrated in the endocardial and epicardial segments.

Reproducibility of perfusion imaging has also been tested in a recent study published by Morton et al(9). 16 patients underwent high-resolution 3T perfusion imaging three times during a single day to evaluate interstudy reproducibility and the effects of diurnal variation. There was reasonable reproducibility of quantitative perfusion measures with a co-efficient of variation of 16, 26.8 and 23.95 (%) for global rest and stress perfusion and MPR respectively. The reproducibility of LV volumes and function was excellent. There were no significant detectable diurnal variations in perfusion or LV volumes or function (p>0.05 for all).

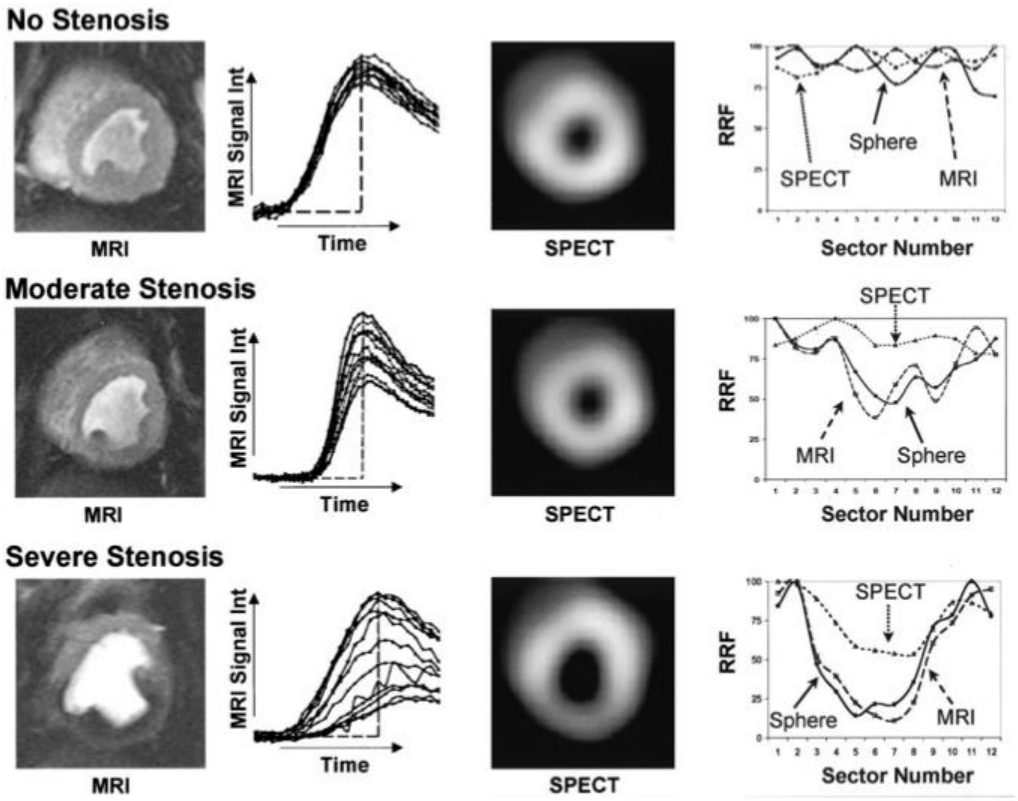


Fig 1.2: CMR, SPECT and microsphere data during pharmacological vasodilatation in animals with no (top), moderate (middle) and severe (bottom) reduction in microsphere flow in the circumflex bed. Shown from left to right are (1) a single frame from the image stack; (2) CMR signal-intensity curves for 12 30-degree sectors (beginning at the most cranial image point and proceeding clockwise); (3) the corresponding 99mTc-sestamibi SPECT image; and (4) relative CMR curve areas, 99mTc-sestamibi count rates, and microsphere concentrations in each 30-degree sector. Peak flow reductions indicated by microspheres are ≥50% and 85%, respectively (lower 2 panels). CMR images show homogeneous myocardial contrast enhancement in the absence of stenosis, moderately reduced enhancement in the circumflex bed with moderate flow reduction, and markedly reduced enhancement with severe flow reduction. A transmural gradient in flow is visually apparent in both cases of flow reduction. CMR signal-intensity curves have nearly identical initial areas in the absence of stenosis. Areas in the circumflex distribution are reduced moderately and markedly with moderate and severe flow reductions, respectively. SPECT images show uniform signal intensity in the absence of flow reduction and in the presence of moderate flow reduction. A prominent perfusion defect is apparent with severe flow reduction. Relative CMR curve areas and microsphere concentrations correspond closely in all cases. SPECT count rates are homogeneous at rest and remain so with moderate flow reduction but show an approximately 50% peak reduction with severe flow reduction. Adapted from (6).

The diagnostic accuracy of CMR perfusion imaging for the detection of functionally significant CAD has been tested in multiple studies with increasingly large patient populations (See table 1.1). There is now convincing outcome (10, 11) data as well as evidence from large prospective studies (5, 12-14).

1.1.2 CMR OUTCOME STUDIES

Two recent prospective studies, comparing CMR perfusion imaging with SPECT, have shown results favourable for CMR. MR-IMPACT I involved 234 patients at 18 centers and compared the results of CMR perfusion imaging with SPECT, having QCA ≥50 % as reference-standard (15). The results of this dose-finding study confirmed the high diagnostic accuracy of CMR and prompted the design of a second trial aiming to directly compare CMR perfusion imaging

and SPECT for detection of CAD, using a similar reference-standard (but this time with the inclusion of previous myocardial infarction but no significant stenosis on coronary angiography as a CAD equivalent). In the MR- IMPACT II trial(12), 533 patients were enrolled in 33 centers. The primary endpoint of CMR non-inferiority vs. SPECT was achieved for sensitivity but not specificity when using the perfusion data only, without information from LGE.

CMR had higher sensitivity (75 % vs. 59 %, P=0.03) and lower specificity (59 % vs. 72 %, P=0.03). Global CMR perfusion imaging diagnostic performance was superior to SPECT for the entire population (465 patients) and in all pre- specified sub-groups such as patients with gated- and non- gated-SPECT, patients without prior myocardial infarction, patients with multi-vessel disease, both in men as well as women(16). Importantly, these results were found using just the CMR perfusion imaging component of the CMR protocol for the direct comparison against SPECT. In clinical practice, however, the functional evaluation of myocardial contractility and evaluation of myocardial fibrosis/scar are routinely performed as part of a comprehensive CMR protocol. Therefore, an even better performance of CMR might be expected when these components are integrated in a comprehensive evaluation.

This was demonstrated in a recent paper published by Greenwood et al(5). They used a comprehensive CMR protocol in a 752 patient single centre study, and compared it to SPECT using coronary angiography as a reference standard. This is the largest CMR perfusion study published so far and demonstrated a sensitivity of 86 % and a sensitivity of 83%, whilst SPECT resulted in 66% and 83% (P<0.0001) respectively.

A meta-analysis published by Hamon et al in 2010(14), involved a total population of 2456 patients, and revealed a per-patient sensitivity and specificity of 89 % and 80 %, respectively. A further meta-analysis of 17, 901 patients showed an area under the curve (AUC) of 0.9055 for CMR (17), which was similar to PET and superior to SPECT imaging. Nandalur et al (18) in another meta-analysis demonstrated a sensitivity, specificity and diagnostic accuracy were 0.91 and 0.81 respectively. A more recent meta-analysis included 14 studies and 12178 patients and specifically addressed prognosis in patients with a normal stress perfusion scan (19). In these patients, the negative predictive value for non-fatal myocardial infarction and cardiac death was 98.12% (95% CI 97.26-98.83).

Recent work is now focusing on novel methods of quantitative perfusion analysis to improve diagnostic accuracy(4, 20). Methods of CMR perfusion analysis continue to attract significant research interest. As mentioned earlier, these include semi quantitative and fully quantitative methods aiming to express myocardial blood flow (MBF) as ml/mg/min. These methods, however, remain within the realm of research.

1.2 Overview of Fractional Flow Reserve

The pressure derived fractional flow reserve allows invasive assessment of ischaemia done at the time of angiography and demonstrates the extent to which maximal myocardial flow is limited by the presence of an epicardial stenosis. FFR is the ratio of maximal myocardial blood flow achievable in the presence of an epicardial stenosis (Qs) to the maximal myocardial blood flow in the hypothetical case of a completely unobstructed coronary artery (Qn).

$$FFR = Qs/Qn$$

Assuming that microvascular and coronary collateral resistances are minimal and constant during maximal hyperaemia, FFR can be derived from simultaneous measurement of distal coronary, aortic and central venous pressures (P_d, P_a, P_v respectively), obviating the need to directly measure myocardial flow(21, 22).

$$FFR = Qs/Qn = (P_d-P_v)/(P_a-P_v)$$

As an unobstructed epicardial coronary artery poses negligible resistance to flow, the normal value for FFR is 1.0 and values below 0.75 reliably predict reversible ischaemia (100% specificity) in patients with normal left ventricular functions. Therefore the FFR value of 0.75 is used to distinguish significant from non-significant stenoses.

1.2.1 FFR VALIDATION STUDIES

The initial validation of the pressure-derived FFR was done with an epicardial coronary doppler probe in a dog model (21). Five dogs were acutely instrumented with an epicardial, coronary doppler flow velocity transducer. FFR was calculated from the pressure

measurements and compared with relative maximum coronary artery flow measured directly by the doppler flowmeter at three different levels of arterial pressure for each of 12 different severities of stenosis at each pressure level (See Fig 1.3).

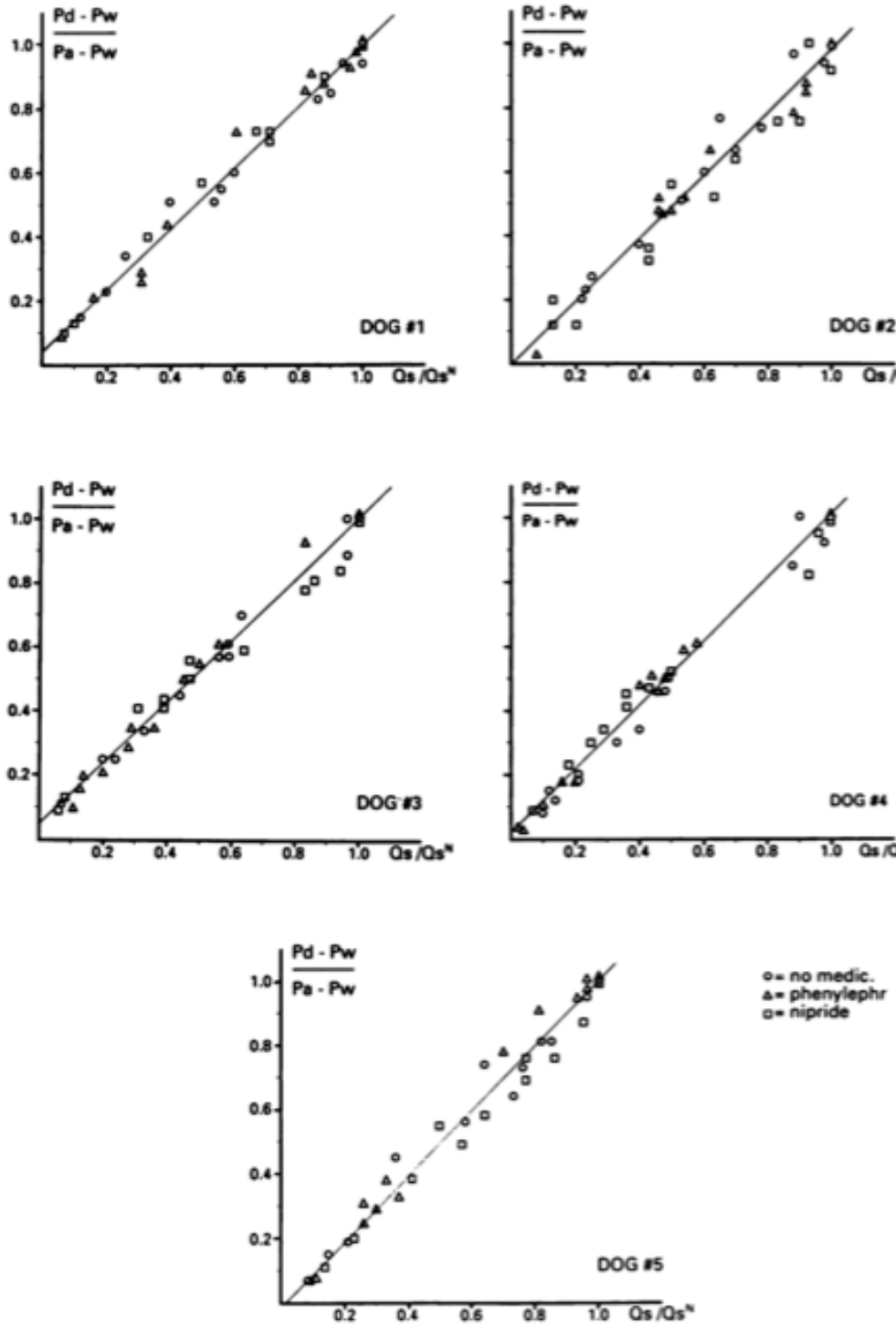


Fig 1.3. Plots of relation between (Pd-Pw)/(Pa/Pw)(pressure derived fractional coronary artery flow reserve) and Qs/Qn (directly measured fractional coronary artery flow reserve) at

different arterial pressures and different stenosis in the five experiments. Pa, mean aortic pressure; Pv, central venous pressure; Pw coronary wedge pressure.

Pijls et al (23) validated FFR in humans with single vessel disease. They defined ischaemia as a positive result on any of three non-invasive tests done in all of 45 consecutive patients: thallium SPECT, stress echocardiography and standard exercise testing. They used this approach to guarantee a high sensitivity for the detection of any ischaemia.

There were a significant number of negative SPECT and stress echo results at FFR values lower than 0.75 although in all patients myocardial ischaemia was demonstrated on one of the three tests used. In 21 of the 25 patients with an FFR of 0.75 or higher, all of the non-invasive tests were negative. Of the remaining three patients, two had a positive exercise ECG and two had a positive thallium scan. In these three patients, the FFR method yielded false negative results, because evidence of inducible ischaemia was present despite an FFR of 0.75 or higher. The authors argue that, according to sequential Bayesian considerations, the composite information from sequentially performed non-invasive tests has a diagnostic accuracy of almost 100%. An FFR < 0.75 yielded a specificity rate for detection of inducible ischaemia of 100%, a sensitivity of 88% and a diagnostic accuracy rate of 93% versus the gold standard of inducible ischaemia on one of three non-invasive tests.

Reproducibility of FFR was tested performing pressure measurements under varying haemodynamic conditions(24). Thirteen patients referred for intervention underwent repeated measurements of FFR, CFR, and the hyperaemic flow versus pressure slope index (IHDVPS) (the slope of the instantaneous hyperaemic diastolic coronary flow velocity-aortic pressure relation) at baseline, during atrial pacing (110 beats/min), during nitroprusside infusion for a drop in systolic blood pressure of 20 mm Hg, and during dobutamine infusion (10 microg/ kg/min). The coefficient of variation for FFR was found to be 4.8%, compared with 10.4% for CFR and 27.7% for IHDVPS. Similar numbers were found for pacing, hypotension, and dobutamine infusion. The reproducibility of FFR with moderate haemodynamic manipulations was found to be robust in these patients, however again this validation was done in patients with single-vessel coronary artery disease (CAD) and normal ventricles.

1.2.2 FFR OUTCOME TRIALS

Although the initial results from the validation study done in humans (23) demonstrated a specificity of 100% and a sensitivity of 88%, subsequent studies have not confirmed such excellent results. A meta- analysis of FFR vs QCA and non-invasive imaging by Christou et al demonstrated a sensitivity and specificity of 76% and 76% of FFR compared with non-invasive imaging in 31 studies (25). Overall concordances were 61% for lesions with diameter stenosis 30-70%, 67% for stenosis >70 % and 95% for stenosis less than 30%. The majority of the non-invasive tests were perfusion scintigraphy with some data available for dobutamine stress echocardiography. Compared to quantitative coronary angiography (QCA) alone, FFR had a sensitivity of 78% and a specificity of 51%. It is noteworthy that there was very poor concordance between FFR and QCA reflecting the significant difference between a purely anatomical and a physiological estimate of ischaemia.

However, using FFR to guide revascularisation has been clearly demonstrated to impact on subsequent event rates in patients. The DEFER (FFR to determine appropriateness of Angioplasty in Moderate Coronary Stenosis) (26) trial showed clearly that in patients with functionally non-significant stenosis (FFR>0.75), the annual mortality or rate of myocardial infarction was less than 1%. 325 patients scheduled for angioplasty were randomised into three groups. If FFR was > 0.75, patients were randomly assigned to the deferral group or the PCI performance group. If FFR was < 0.75, PCI was performed as planned and patients were entered into a reference group. Overall, the event-free survival was not different between the deferred and performed groups (80% and 73%, respectively, p = 0.52), and both were significantly better than in the reference group (63%, p = 0.03). The composite rate of cardiac death and acute myocardial infarction in the deferred, performed, and reference groups was 3.3%, 7.9%, and 15.7%, respectively (p = 0.21 for deferred vs. performed and p = 0.003 for reference vs. both of the deferred and performed groups. The percentage of patients free from chest pain on follow up was not different between the deferred and performed groups. Thereby concluding that it is safe to defer lesions with a negative FFR for up to five years (27)(See fig 1.4).

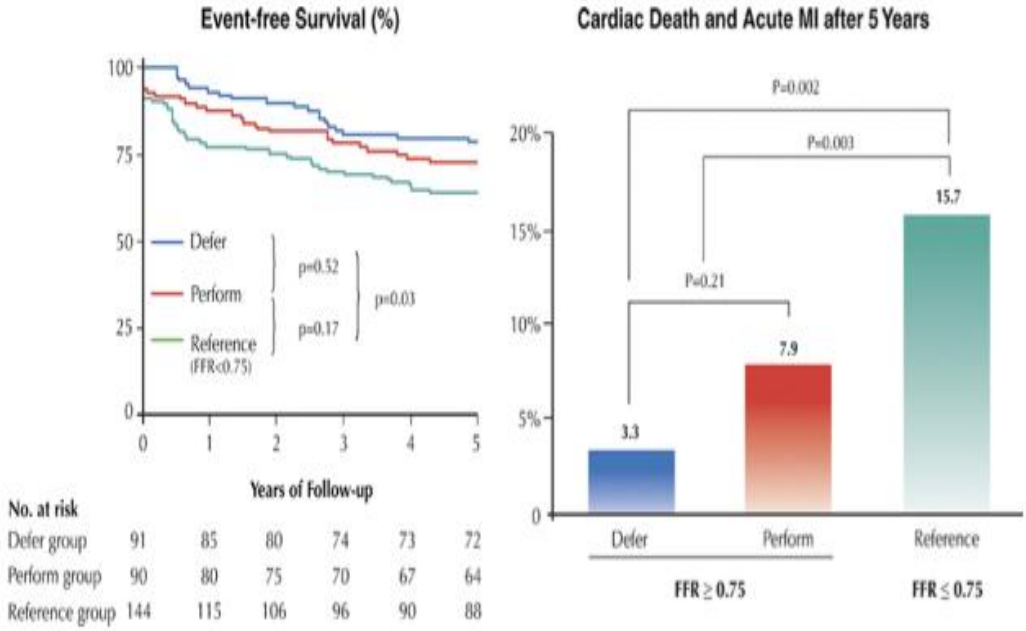


Fig 1.4: Data from the DEFER study: 5-year follow-up study.

(Left) Event free survival curves for the DEFER, Perform, and reference groups.

(Right) incidence of cardiac death/myocardial infarction (MI) for the three groups. Adapted from (28)

Furthermore, the FAME trial (29) showed that in 1000 pts with angiographic multivessel disease, in whom the decision to stent was based on the FFR measurement alone (FFR <0.80), the rate of adverse events were decreased by 30% in the first year after FFR guided PCI in multivessel disease. In this randomised controlled trial, operators randomised all electively selected lesions for PCI into an angiography guided or PCI guided approach based on an FFR value of less than 0.80 demonstrated a one year event rate of 18.3 % in the angiography group, and 13.2% in the FFR group (p=0.02). After 2 years, the advantage of FFR guidance of PCI in multivessel disease increased further with respect to lower mortality and myocardial infarction rates. This trial clearly demonstrates that diameter stenosis is not a good marker of significance of disease and that treatment should be guided according to functional evaluation. The reduction in event rates is likely to be related to fewer implanted stents having fewer procedure-related early and late stent complications.

Many of the earlier FFR and certainly most of the validation studies used an FFR value of 0.75 or below as the threshold for significance. The newer studies all use a threshold of 0.80 incorporating the traditional "grey-zone" between 0.75 and 0.8. The rationale behind this decision is not clearly stated and it does raise the question of whether the results of the initial validation trials show the same high diagnostic accuracy with the use of a different threshold for significance.

The FAME 2 trial (30) is a prospective multicentre RCT comparing FFR guided PCI and medical therapy with medical therapy alone in lesions with an FFR result of less than 0.8. This trial enrolled 1220 patients but was halted early. Patients with stable CAD (11% asymptomatic, 16 % with silent ischaemia, 66 % with class 1- 2 symptoms) for whom PCI was being considered, had all stenoses assessed by FFR (76% had single vessel disease by FFR). The primary end point was a composite of death, myocardial infarction, or urgent revascularisation

Recruitment for this trial was halted prematurely because of a significant between group difference in the percentage of patients who had a primary endpoint event (4.3% vs 12.7%). This was largely driven by a difference in the rate of urgent revascularisation with 50 % of these patients having an unstable event. Neither the rate of death or the rate of myocardial infarction differed significantly between the two groups. There were only 33 "hard events" of which there were only 4 deaths (3 in the OMT arm; 1 in the PCI arm) and 29 MI's (14 in the OMT arm; 15 in the PCI arm). Of note, the urgent revascularisation end-point was largely a clinical one and did not require objective evidence of either abnormal biomarkers or electrocardiographic ischaemia in all patients to meet this endpoint. Of the 56 unplanned hospitalisations resulting in urgent revascularisation, 29 (52%) were not accompanied by any objective findings of high-risk ischaemia or biomarker positivity. Due to the early termination, the effect of PCI on symptom reduction was not shown to be significant beyond 6 months. It seems therefore that the benefit of PCI over OMT was not demonstrated in terms of hard events or symptoms, thereby again fuelling the controversy surrounding the advantages of PCI.

1.3 STUDIES OF DIRECT COMPARISON BETWEEN CMR AND FFR

There have been a number of comparative studies between CMR and FFR, predominantly for the validation of CMR perfusion imaging against FFR for discrimination of the haemodynamic significance of intermediate stenosis (see table 1.1 for a list of comparative trials). In a population of 101 patients with suspected angina, Watkins et al reported an excellent per-patient sensitivity (95 %) and specificity (91 %) for detection of FFR ≤0.75, stating that CMR performance seems to be even higher than previously reported(31). Jogiya et al assessed 53 patients with 3D whole heart perfusion CMR and FFR in vessels with > 50 % severity angiographically(32). The sensitivity, specificity, and diagnostic accuracy of CMR for the detection of CAD were 91%, 90% and 91% on a per patient basis. Bettencourt et al confirmed these findings, reporting a per- patient sensitivity and specificity of 93 % and 87 % respectively, using the same FFR threshold as reference and values of 89 % and 88 % using an FFR threshold of 0.80 which is most commonly used in current clinical practice (33). Both studies showed better results in vessel- and patient- based analysis when the functional standard (FFR) was used as opposed to QCA, suggesting that the accuracy of CMR performance is underestimated when compared with an anatomical reference-standard.

Further developments are continuously being reported in the field of CMR. Whole-heart 3D dynamic perfusion allows determination of the myocardial ischaemic burden holding the promise for better non-invasive therapeutic guidance and risk stratification.

Table 1.1: Major CMR, FFR and comparative trials

	Year	No of patients	CAD prevalence (%)	Reference standard	Sensitivity	Specificity
Nagel et al(11)	2003	84	51	CXA≥75%	88	90
Ishida et al(34)	2003	104	74	CXA≥70%	98	95
Doyle et al(35)	2003	185	14	CXA≥70%	57	78
Plein et al(36)	2004	68	82	CXA>70%	96	83
Takase etal(37)	2004	102	75	CXA>50%	93	85
Giang et al(38)	2004	44	64	CXA≥70%	93	75
Plein et al(39)	2005	82	72	CXA≥70%	88	74
Klem et al(40)	2006	92	40	CXA≥70%	89	87
Pilz et al(41)	2006	171	66	CXA>70%	96	83
Merkle et al(42)	2007	228	67	CXA>70%	96	72
Schwitter et al(15)	2008	225	76	CXA≥50%	85	67
Gebker et al(43)	2008	101	69	CXA≥50%	90	71
Klem et al(40)	2006	92	27	CXA≥50%	89	87
Klein et al(44)	2009	78	69	CXA>50%	67	88

Arnold et al(45)	2010	62	66	CXA>50%	90	81
Stolzmann et al(46)	2011	65	60	CXA≥50%	78	88
De Mello et al(47)	2011	54	69	CXA≥70%	92	84
Gebker et al(43)	2012	78	69	CXA≥70%	92	83
Schwitter et al(12)	2012	425	49	CXA≥70%	67	61
Greenwood et al(5)	2012	752	39	CXA	86	83
FFR studies						
Pijls et al(48)	1995	60		X ECG	BCV	0.74
De Bruyne et al(49)	1995	60		X-ECG	BCV	0.72
Pijls et al (23)	1996	45		X-ECG/SPECT/PACING/DSE	88%	100%
Bartunek et al(50)	1997	37		DSE	BCV	0.68
ABE et al(51)	2000	46		SPECT	83%	100%

Chameleau et al(52)	2001	127		SPECT	BCV	0.75
Caymaz et al(53)	2000	40		SPECT	91%	100%
Jimenez-Navarro et al(54)	2004	21		DSE	n/a	n/a
Usui et al(55)	2003	167		SPECT	79%	79%
Meuwissen et al(56)	2002	151		SPECT	Predictive accuracy	74%
De Bruyne et al(57)	2001	57		MIBI-SPECT post MI	82	87
Samady et al (58)	2006	48		MIBI-SPECT post MI	88	93
CMR vs FFR						
Rieber et al(59)	2006	43	31	FFR ≤ 0.75	93	57
Costa et al(60)	2007	30	32	FFR ≤0.75	93	57
Futamatsu et al(61)	2007	30	32	FFR ≤0.75	93	57

Watkins et al(31)	2009	101	77	FFR ≤0.75	95	91
Kirschbaum et al(62)	2011	50	43	FFR <0.80	97	60
Lockie et al(63)	2011	42	42	FFR ≤0.75	82	94
Bettencourt et al(33)	2012	103	44	FFR ≤0.80	89	88
Bernhardt et al(64)	2012	34	62	FFR ≤0.80	90	100
Jogiya et al(32)	2012	53	64	FFR ≤0.75	91	90
Manka et al(65)	2012	109	58	FFR ≤0.75	90	82

1.4 ASSESSMENT OF ISCHAEMIC BURDEN

Whilst CMR and FFR may be accurate and reproducible measures of ischaemia, whether ischaemic extent is the important variable to be considered in decisions regarding revascularisation is now also being considered.

Hachamovitch (66) assessed survival in 10 627 patients who had undergone clinical SPECT studies in a single US centre. Patients with no or mild baseline ischaemia had an improved prognosis with medical therapy compared with revascularisation, while conversely those with moderate-to-severe ischaemia had an improved prognosis with revascularisation. An ischaemic threshold of 10– 12.5% of myocardium differentiated patients who benefited from revascularisation from those who did not (fig 1.5). The relationship between % ischaemic myocardium and the log of the hazard ratio for revascularisation versus medical therapy based on this Cox model (fig 1.5) revealed that in the setting of no or mild amounts of inducible ischemia, patients undergoing medical therapy had a survival advantage over patients undergoing revascularisation. These 2 lines intersect at a value of approximately 10% to 12.5% ischaemic myocardium, above which the survival benefit for revascularisation over medical therapy increases as a function of increasing amounts of inducible ischaemia. Even though these data are from a very large cohort and the conclusions are interesting, there are inherent limitations to the study as it was a non- randomised, retrospective observational study that used a propensity score to adjust for non-randomisation.

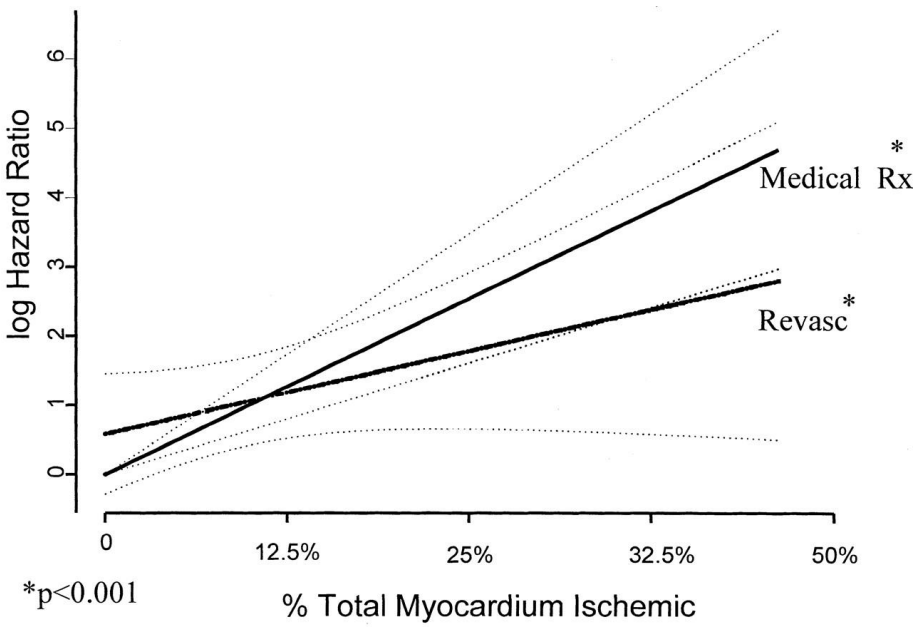


Figure 1.5: Relationship between myocardial ischaemia burden and the hazard ratio for cardiac death in patients treated with revascularisation (Revasc) versus medical therapy (Medical Rx). A threshold of 10-12% ischaemia burden defines those who appear to derive a prognostic benefit from revascularisation; adapted from (66).

The landmark randomised controlled COURAGE trial (67) on the other hand concluded that there is no prognostic benefit from PCI in addition to optimal medical therapy as an initial treatment for stable CAD. This was despite the fact that the majority of participants had objective evidence of ischaemia at baseline, including 54% of patients with reversible defects on nuclear imaging.

These data generated considerable controversy and led many to re-evaluate entirely the role of PCI in stable CAD. It seems paradoxical that there was no incremental benefit from PCI given that the presence of demonstrable ischaemia confers a worse prognosis. Although there are a number of possible explanations for this, the most likely is because the study design favoured inclusion of lower risk patients with a lower burden of pre-treatment myocardial ischaemia. For example, patients with an exercise test positive in the first stage were excluded and only a third of patients in the PCI arm had a significant reduction of ischaemia following PCI.

In apparent contradiction to the main study, the nuclear substudy of the same trial (68) suggested that PCI might confer a prognostic benefit in patients with a significant ischaemic burden and improved patient selection may allow this benefit to be realised.

In a more recent observational study by Hachamovitch et al (69), 13 969 patients who underwent adenosine or exercise SPECT, were identified and a percentage ischaemic myocardium and percentage fixed myocardium was calculated. These patients were then followed up and those patients with a high ischaemic percentage and without prior myocardial infarction (MI) demonstrated a benefit from early revascularisation. This benefit was not evident in those patients with prior scarring. The survival of patients with minimal ischaemia was superior with medical therapy without early revascularisation.

These studies form part of the emerging evidence that for patients to really derive prognostic benefit from revascularisation, an approach geared towards significant ischaemia reduction should be adopted.

1.4.1 INVASIVE ASSESSMENT OF ISCHAEMIC BURDEN

Both FFR and invasive angiography are limited in that they don't allow direct measures of ischaemic burden.

To overcome this limitation several jeopardy scores have been developed and validated (70, 71). These scores are based on the location and anatomical severity of coronary lesions; however, they do not incorporate the functional significance of a stenosis.

The APPROACH (72) anatomical score divides the left ventricle into regions according to pathological studies in humans evaluating the relative proportion of myocardium perfused by each coronary artery. In the modified version, the vessel dominance, site of occlusion and size of the major branches of the infarct related artery are taken into consideration.

The BCIS score is a contemporary score(71, 73), derived from the Duke score. The Duke Jeopardy score is calculated by dividing the coronary tree into six segments of nearly equal myocardial perfusion (i.e. left anterior descending artery, major septal perforator, major diagonal branch, circumflex artery, major obtuse marginal artery and posterior descending

artery). A score of two is given for each significant lesion in a myocardial territory. The BCIS score allows for the classification of graft and left main stem disease by ascribing points to a left main lesion of >50% and to significant graft lesions.

Although there are a number of different jeopardy scores, their use is mainly confined to research applications.

1.4.2 CMR ASSESSMENT OF ISCHAEMIC BURDEN

Most of the studies using ischaemic burden have traditionally used SPECT as the non-invasive imaging modality. There is some evidence(74) that the prognostic threshold for significant ischaemia applies to CMR also, but there are no direct comparative trials related to this. In preliminary analysis of 10 patients who underwent CMR and SPECT scanning, the mean percentage of inducible ischaemia was 7.3% (range 0-22.2%) for CMR and 10.3% for SPECT (range 0-25.0%). Overall there was no significant difference (P=0.47) (74)

In a recent study, Jogiya et al measured ischaemic burden by visual analysis of CMR images(75) demonstrating good correlation with the Duke Jeopardy score (r=0.82). Morton et al showed that a BCIS score ≥6 predicts an ischaemia threshold of 12% on CMR with high specificity (76). However, both of these studies have used an anatomical score, without correction for haemodynamic relevance and, as mentioned earlier, the concordance between anatomical severity and physiological evaluation by FFR is poor.

Manka et al (65) used 3D perfusion technique to compare the FFR significant lesions with the volume of myocardial hypo-enhancement. They found that a cut off value of 4.4% ischaemic burden corresponding to a FFR threshold of 0.75 resulted in a sensitivity and specificity of 86.5% and 86.3% respectively.

CHAPTER 2: AREAS OF DISCREPANCY BETWEEN CMR AND FFR

There are important fundamental differences in the measurement of ischaemia by CMR and FFR. FFR is primarily a method of vessel specific lesion assessment and CMR perfusion imaging focuses on the effect of a functionally significant stenosis on myocardial blood flow. CMR perfusion imaging gives an indication of Coronary Flow reserve (CFR), which reflects the combined impact of epicardial and microvascular resistance on limiting hyperaemic blood flow. Because of the different nature of assessment there are certain clinical scenarios in which the results of these two tests will differ.

In this chapter, the areas of potential discrepancy will be reviewed.

2.1 MICROVASCULAR DISEASE

A common area that can cause discrepancy between the results of non-invasive and invasive tests is in coronary microvascular disease, in which functional and structural abnormalities of the coronary microvasculature can lead to microvascular ischaemia.

Microvascular disease is defined as reduced coronary flow reserve in the absence of an epicardial stenosis and can be primary or secondary. Primary microvascular disease occurs in the absence of any other cardiac cause and the underlying disorder is thought to be due to vascular abnormalities of the endothelial cells, smooth muscle cells and the autonomic nervous system resulting in raised microvascular resistance. Secondary microvascular disease can occur due to conditions such as hypertension, hypercholesterolaemia, left ventricular hypertrophy and diabetes. Similar mechanisms are at play in patients with risk factors for CAD. Left ventricular hypertrophy is also thought to result in raised microvascular resistance due to increasing myocardial fibrosis. Furthermore, having epicardial coronary disease itself is associated with concomitant microvascular disease.

2.1.1 CMR IN MICROVASCULAR DISEASE

With CMR perfusion imaging, stress perfusion imaging relies on the difference between hyperaemic and baseline blood flow, the CFR. CFR reflects the combined impact of epicardial

and microvascular resistance on limiting hyperaemic flow, therefore conditions affecting myocardial and microvascular resistance such as age, left ventricular hypertrophy, diabetes mellitus, or myocardial infarction will affect the value of CFR, independent of epicardial coronary disease.

It is therefore plausible that in patients with significant microvascular dysfunction, a perfusion defect demonstrating ischaemia may be visible in the absence of significant epicardial disease. This group of patients would be similar to the patient group studied by Meuwissen et al (77) in which FFR was > 0.75 but CFR was <2.0, reflecting higher microvascular resistance (see Fig 2.1).

However, whether patients with microvascular disease and normal coronary arteries, do have myocardial ischaemia is heavily debated. This conflict is epitomised by SPECT perfusion data in patients with syndrome X, with some studies showing abnormal perfusion in the majority of these patients(78)and others showing no correlation between perfusion defects and CFR(79).

The capability of CMR itself for detecting subendocardial ischaemia, in microvascular disease is also unclear, despite the superior spatial resolution. A study by Panting et al (80)showed that patients with angina and normal coronary angiography have a reduction in the ratio of subendocardial to subepicardial myocardial perfusion on CMR, suggesting ischaemia is the cause of symptoms in this patient group. However, Vermeltfoort (81) in a similar study design using CMR found no difference in subendocardial and subepicardial perfusion in response to adenosine. The reason for the contrasting findings is not clear but it has been suggested the findings seen in the Panting study may have been due to an artefact of the first pass sequence(82).

Lanza et al (83) showed that dobutamine induced stress abnormalities in the left anterior descending artery (LAD) territory at peak stress in cardiac syndrome X (CSX) patients were associated with a reduced CFR in the LAD (measured by transthoracic echo doppler study) in response to adenosine suggesting microvascular dysfunction as an aetiology.

In another study by Yilmaz et al (84) symptomatic patients with normal coronary arteries underwent CMR perfusion testing, coronary angiography and achetylcholine testing in 42

patients. They found that, during intracoronary acetylcholine testing, those patients with a reversible stress induced perfusion defect were more likely to have a coronary epicardial or microvascular vasoreaction (20/22). Those without a perfusion defect were less likely to have a reaction to acetylcholine (10/20).

In contradistinction to the above study, a recent study by Karamitsos (85) et al, examined 18 patients with CSX chest pain, abnormal exercise test, normal coronary angiogram without other causes of microvascular dysfunction and assessed oxygenation with a BOLD sequence and also quantified myocardial blood flow. There were no significant differences in MBF at stress, BOLD signal change and coronary flow reserve measurements in CSX patients and controls respectively. The only significant difference demonstrated between the two groups was that the group with syndrome X experienced more chest pain. This study is interesting as the patients are characterised very well however, rather than finding conclusive answers, it does add further fuel to the debate regarding this difficult patient group.

2.1.2 FFR IN MICROVASCULAR DISEASE

By definition, primary and secondary microvascular disease occur in the presence of normal coronary arteries. Therefore, in the absence of epicardial coronary stenosis, the FFR will be negative.

However, consideration needs to be given to the assessment of epicardial disease in the presence of increased or variable microvascular resistance. For the accurate interpretation of FFR in this scenario it is important to recapitulate how FFR has been derived.

FFR myo = Qs/Qn

Which equates to the fraction of maximal flow to the myocardium in the presence of a stenosis (Qs) to the theoretical maximal flow in the same myocardial bed without a stenosis (Qn).

According to Ohms law, **Flow= pressure /resistance (Q= P/R)**

FFR myo =Qs/Qn = (Ps/Rs)/ (Pn/Rn)

Furthermore, Ps is defined as the measure mean pressure distal to a stenosis (Pd) minus mean venous pressure (Pv). Pv here is an estimate of residual myocardial capillary perfusion pressure. The same applies to Pn

FFRmyo = Qs/Qn = (Pd-Pv)/r

(Pa-Pv)/r

Also, during maximal hyperaemia, it is assumed that *myocardial resistance of a stenotic bed, Rs, or a normal bed Rn would be minimal, constant and comparable.*

Therefore R cancels from the equation, and if venous pressure is assumed to be small then the equation approaches

FFRmyo = Pd/Pa

It is important to understand that the measurement of FFR is based on a number of assumptions such as myocardial resistance is negligible and constant and that venous pressure is small. As mentioned earlier, most of the human FFR validation studies were done in patients with single vessel disease and normal ventricular function. In patients with more complex disease i.e. multivessel disease or with reduced ventricular function, microvascular resistance is more likely to be raised, inconstant or heterogeneous.

Even in the absence of coronary narrowings, there is a huge variation in microvascular resistance between patients and even between coronary territories. In a study by Meuwissen et al (77), 150 lesions (between 40% and 70% diameter stenosis by visual stenosis) in 126 patients were assessed with FFR and CFR. Agreement between outcomes of FFR and CFR, categorised at cut-off values of 0.75 and 2.0 respectively, was observed in 109 coronary lesions (73%). In 27% of lesions there was a discrepancy between FFR and CFR (See Fig 2.1). In the group where FFR was >0.75 and CFR < 2.0, there was a significantly higher measured microvascular resistance (defined as the ratio of mean distal pressure to average peak blood flow velocity during maximal hyperaemia) (overall range 2.42±0.77 vs1.91±0.70 mmHg.cm^{-}

$^{1}.s^{-1}$). There also was a significant variability in the measured microvascular resistance (overall range 0.65 to 4.64 mmHg.cm$^{-1}.s^{-1}$). This suggests that if microvascular resistance increases then CFR will decrease and FFR will increase despite an anatomically fixed stenosis. The variability in microvascular resistance exists across individuals and perfusion territories. This study challenges the notion that microvascular resistance is constant and negligible and emphasises the importance of combined pressure and flow velocity measurements to evaluate coronary lesion severity and microvascular involvement.

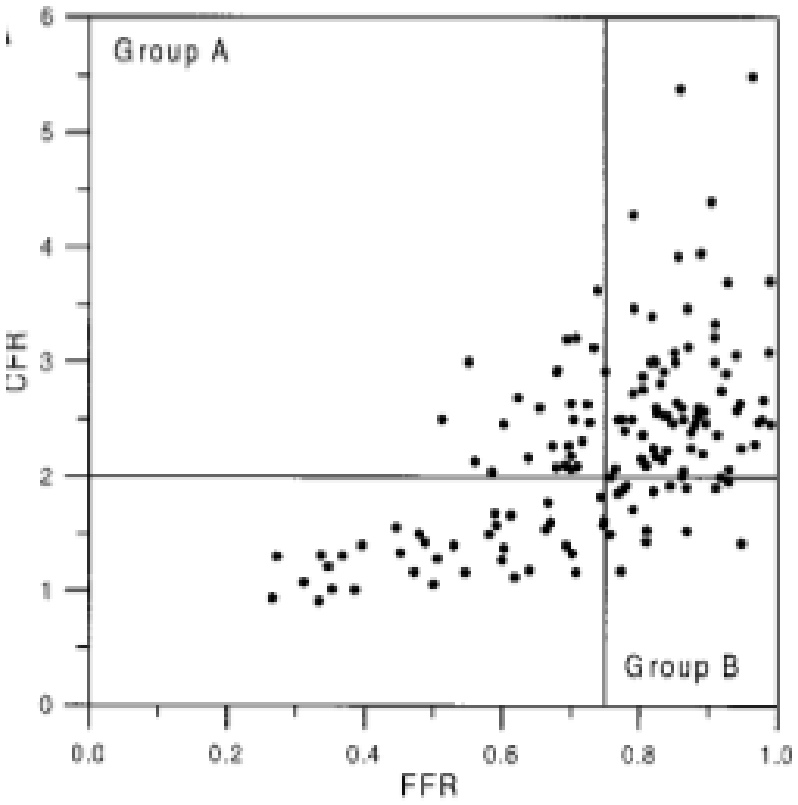


Fig 2.1: Scatterplot of FFR vs CFR (n=150). Data were categorized on basis of cut-off values. Group A had FFR<0.75 and CFR≥2.0; Group B had FFR ≥0.75 and CFR<2.0. Adapted from (77).

The effect of varying microvascular resistance means that the assumptions underlying the calculation of FFR may not always be correct, and FFR may not be accurate when microvascular resistance is not constant and minimal. In these cases there may be significant discordance between CFR and FFR measurement. Although the population studied by

Meuwissen et al (77) was fairly diverse including patients with diabetes mellitus, hypertension, left ventricular hypertrophy and restenosis, it is interesting to surmise whether in patients with higher levels of comorbidity and diffuse disease, concordance is worse. If microvascular resistance is variable in the presence of diffuse coronary disease, distal coronary pressure in the stenotic bed is likely to be higher than that in the proximal bed that will lead to a higher FFR value, independent of stenosis severity.

Chameleau et al (86) investigated the effect of the severity of an epicardial stenosis on microvascular resistance in 27 patients with coronary artery disease and stable angina. All patients had an angiographically normal coronary artery, an artery with an intermediate lesion, and an artery with a severe lesion: the latter was treated with angioplasty. The ratio of mean distal pressure to average peak blood velocity was used as an index of microvascular resistance. They demonstrated that there was a positive association between coronary lesion severity and variability of distal microvascular resistance that normalizes after angioplasty. Additionally, there was also heterogeneity of microvascular resistance between perfusion territories.

This finding is further tested in a study by De Luca et al(87) who used increasing doses of intracoronary vasodilator and assessed the effect of progressive vasodilatation on FFR. FFR was assessed in 50 intermediate lesions in 46 patients with increasing doses of adenosine up to 720Ug administered as intracoronary boluses. Increasing doses of adenosine progressively decreased FFR values and increased the percentage of patients showing an FFR <0.75. In addition, lesion length and stenosis severity were independent angiographic determinants of FFR.

Whether these theoretic concerns make a clinical difference requires more thorough validation of FFR in different coronary and microvascular physiological disease states.

2.2 MULTIVESSEL DISEASE

Although there are extensive validation studies for both FFR and CMR perfusion, there is less data available for diagnostic accuracy of the two tests specifically in multivessel disease. This

assessment can be more complex due to the presence of raised and variable microvascular resistance and other co-morbidites and risk factors.

2.2.1 CMR IN MULTIVESSEL DISEASE

The diagnosis of functional significant coronary artery disease in patients with multi-vessel disease has traditionally been seen as a challenge for non-invasive imaging tests.

Most previous studies specifically aimed at patients with multi-vessel disease have predominantly used SPECT as the non-invasive imaging test. In a study by Lima et al (88) in 143 patients with proven angiographic 3–vessel CAD, myocardial perfusion imaging with SPECT demonstrated no significant perfusion defect or a single vessel pattern of disease in only 54% of patients. This may be due to the lower sensitivity of SPECT, which has been attributed to its relatively low spatial resolution(89) or to the well-recognised disparity between angiographic and functional information (90). The actual prevalence of true functional vs angiographic three vessel disease is low and in the FAME cohort of patients, only 14% of the angiographically classified 3- vessel disease group had functional 3- vessel disease(91). Additionally in the FAME 2 cohort of patients, only 3% of the patients had 3-vessel disease by FFR. The low numbers make the characterisation and analysis of a true functional multivessel disease patient group more difficult.

The data on CMR in multivessel disease is limited with most studies assessing multi-vessel disease only as a subgroup analysis in larger studies

The CEMARC study, a large (728 pts) single centre study showed a sensitivity of 86% for CMR which was significantly superior to that of SPECT at 66.5%, although specificity was similar (5). Subgroup analysis for multivessel disease in the CEMARC trial resulted in good diagnostic accuracy (AUC of 0.91 vs 0.77 for SPECT), however the assessment was on a per patient basis only and anatomic stenosis severity rather than FFR was used as the reference standard. Subgroup analysis in the MR-IMPACT 2 study considering multi-vessel disease, by different gender and in patients without prior MI confirmed superior diagnostic accuracy(16). This was a multivendor trial in which 533 patients in which patients had SPECT, coronary angiography, and CMR in all patients. They demonstrated that the sensitivity of CMR to detect CAD was

superior to SPECT and the specificity was inferior to SPECT. A subgroup analysis was done of patients who had multivessel disease, and they demonstrated superiority of CMR to SPECT in patients with multi vessel disease. See Fig 2.2

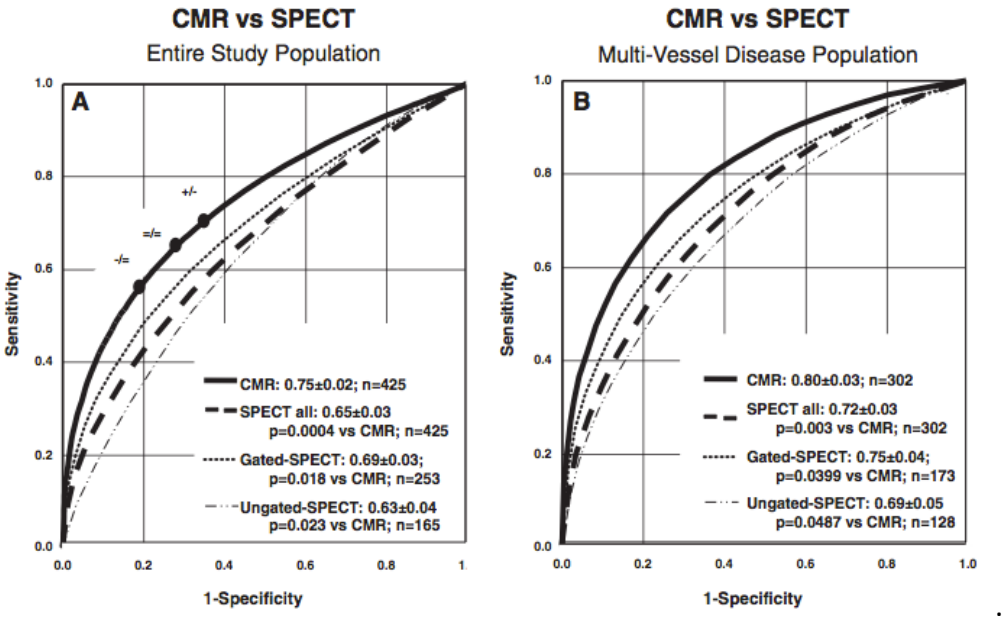


Figure 2.2: Diagnostic performance in the entire MR IMPACT II study population – ROC analyses. Diagnostic performance of perfusion-CMR and SPECT imaging compared by receiver operating characteristics curves (ROC) analyses for detection of CAD (per patient analysis). A). CMR performs superior to all SPECT studies in 1–3 vessel disease (1–3 VD) patients and is also superior to the gated-SPECT and ungated-SPECT groups. Difference in AUC between gated-SPECT and ungated-SPECT did not reach statistical significance. The dots on the ROC curve for CMR indicate the sensitivities and specificities for various thresholds (i.e. at summed gradings of 23 [dot on the left, 21 [middle dot], and 19 [dot on the right]) with + and – indicating superiority and inferiority vs SPECT, respectively, and = indicating non-inferiority versus SPECT for both, sensitivity and specificity, as defined as primary end-point of the study B): Perfusion-CMR is superior to SPECT in multi-vessel disease patients. Sub-group analyses for gated-SPECT and ungated-SPECT yielded superiority for CMR, as well (adapted from(12)

A comparative accuracy study done by Chung et al (92) compared SPECT and perfusion CMR in patients with angiographic three vessel disease and showed that CMR detected perfusion defects in all three vascular territories in 57% of patients vs only 11% with SPECT.

Although this suggests that CMR performs better than SPECT in multivessel disease, there is still paucity of specific data on the accuracy of CMR in multivessel disease, in particular, the assessment of diagnostic accuracy on a per vessel basis (Fig 2.3). Although the higher spatial resolution afforded by CMR should improve the diagnostic ability of CMR to accurately detect multivessel disease, further evidence is required before CMR can be recommended for guidance of revascularisation strategy in multi-vessel disease.

Fig 2.3: Example of CMR and angiographic images of patients with multivessel disease. In this case the LAD FFR was 0.7, the Cx was a CTO and the RCA FFR was 0.68. The CMR images show a mid ventricular slice demonstrating both an inferior and an anterior territory perfusion defect. A Cx artery defect is not well visualised and this may be due to the presence of collaterals.

2.2.2 FFR IN MULTIVESSEL DISEASE

The FAME trial (90) demonstrated that stenting in multivessel disease with FFR guidance results in fewer adverse events (death, non fatal MI and repeat revascularisation) than with angiography guidance. It has been suggested that this is likely to be due to a reduction in stent usage leading to a reduction in events, due to less side branch occlusion or embolisation and stent thrombosis. Although this suggests that an FFR guided strategy is superior to an angiography guided strategy the utility of stenting in multivessel disease needs to be examined more closely.

One of the advantages of FFR is that it allows precise localisation of the lesion causing ischaemia, which is thought to be superior to the spatial resolution of non-invasive imaging. Every artery or segment is analysed separately, and potential masking of one ischaemic area by another, more severely ischaemic zone is avoided. However, the utility of FFR to guide complete revascularisation as opposed to a "targeted revascularisation" approach needs to be considered.

The COURAGE trial(67) failed to show a benefit for revascularisation when compared with optimal medical therapy, albeit in a low risk population with non-complex CAD. PCI was only beneficial in terms of ischaemia reduction in patients with significant ischaemia at the start. Thus there is an emerging concept that a favourable prognosis results from substantial ischaemia reduction rather than complete anatomical revascularisation.

In the FAME trial (90), the main difference between the angiography and the FFR guided groups was a difference in the primary endpoint of mortality and myocardial infarction with no significant difference in angina reduction between the two groups (76% vs 80% free form angina at two years) (91).

As alluded to earlier, the higher rate of death and myocardial infarction may be related to the increased number of stents used in the angiography guided vs FFR guided strategy (2.7 vs 1.9 stents per patient respectively). Although there is clear demonstration that an FFR guided strategy is better than an angiographic strategy as it reduces the amount of excessive stent usage, there is no evidence that stenting in itself leads to symptomatic improvement or improved prognosis.

Thus, it is possible that targeting revascularisation of lesions with a high ischaemic burden further, both within the multi-vessel and single vessel cohort could be beneficial in terms of symptom reduction as well as further reducing stent utilisation. Although ambitious, there is also the potential to aim for the elusive goal of prognostic benefit.

The recent FAME 2 trial(30) does not provide any further clarification by essentially demonstrating that in FFR positive lesions, PCI is better than medical therapy as it reduces the need for urgent revascularisation driven by acute events. The impact on hard end-points such as mortality is not demonstrated due to the premature termination of the trial.

However, what the trial does allude to is a potential difference in outcomes related to different FFR values. The benefit of PCI seemed to be more pronounced among patients who had lesions with an FFR of less than 0.65 than among the patients who had only lesions with larger FFR values. This would be presumed to be due to a larger ischaemic burden associated with a lower FFR value. The mean FFR value in both groups was 0.68.

This suggests that the extent of ischaemia reduction rather than the stenting of all FFR positive lesions is the important variable leading to patient benefit. With this in mind, a targeted approach dealing with the most severe lesion may be of more benefit than stenting all FFR positive lesions in a multivessel disease setting. The associated reduction in stent usage with this approach will no doubt be beneficial.

In addition to FFR being used preferentially to target lesions causing more severe ischaemia, the accuracy of FFR measurement in multivessel disease also needs to be considered. This requirement for multivessel assessment can occur both within the context of stable and unstable CAD.

In the elective setting, there is a paucity of data regarding the utility of FFR to guide revascularisation strategies. One concern is the presence of abnormal microvascular resistance, as discussed earlier, which is more likely to be prevalent in this cohort of patients with complex CAD. One small study (93) has demonstrated that elective target vessel PCI increases non-target vessel FFR due to an increase in remote coronary microvascular resistance in patients with normal microvascular function. This is thought to be due to generalised vaso-constriction mediated by the adrenergic system and should be taken into consideration when interpreting borderline FFR result in the diagnostic grey zone especially for FFR assessments that are planned immediately after initial stent implantation.

2.3 MYOCARDIAL INFARCTION

The assessment of ischaemia after myocardial infarction is more complex than that undertaken in an elective setting. There are additional issues to consider such as the assessment of bystander disease that is seen in up to 40% of patients, and the impact of myocardial scarring.

2.3.1 CMR IN MYOCARDIAL INFARCTION

In the early phase after myocardial infarction, CMR is mainly used for the assessment of viability, residual ischaemia and also for the identification of any early mechanical complications.

For the early assessment of bystander disease, adenosine stress CMR has been shown to be safe and feasible early after primary PCI and can reliably assess co-existing disease in non-culprit arteries (94). Additionally, there is data which shows that post PCI (3 days) CMR via visual assessment can identify perfusion defects with 96% sensitivity, 50% specificity, 97% positive predictive value, 43% negative predictive value(95). The low specificity in this study was explained by the high prevalence of diabetes (16%), hypertension (40%) and hypercholesterolemia (32%) causing microcirculatory dysfunction. In addition, the presence of acutely injured myocardium or variable amounts of scar was thought to have an unpredictable effect on the visual interpretation of myocardial perfusion. This is an interesting finding as it suggests that the presence of microvascular dysfunction in these patients may affect the CMR interpretation then it is likely to affect the FFR results also.

One of the real strengths of CMR, however, is in demonstrating areas of scar in patients with chronic myocardial infarction. This has been demonstrated to be a well-validated and robust technique. The seminal paper by Kim et al (96) demonstrated that with delayed enhancement imaging it was possible to predict reversible myocardial injury, which would improve after revascularisation. In this study 50 patients had CMR before and after revascularisation. Contractility increased in 256 of 329 segments (78 percent) with no hyperenhancement before revascularisation, but in only 1 of 58 segments with hyperenhancement of more than 75 percent of tissue. In particular, the identification of an epicardial rim of scar is not possible with any other forms of imaging and is important for both diagnostic and prognostic purposes. The performance of late gadolinium enhancement imaging CMR (LGE) for the detection of MI has also been tested in an international multicentre trial(97). In total, 282 patients with acute and 284 with chronic first-time MI were scanned in 26 centres throughout the U.S., Europe, and South America. The study showed that the sensitivity of LGE increased with increasing gadolinium dose, reaching 99%

and 94% in acute and chronic MI. Furthermore, when MI was identified, it was in the correct location in more than 97% of patients (i.e., the location of hyperenhancement matched the perfusion territory of the infarct-related artery).

Although the interpretation of the extent of ischaemia could potentially be more problematic with a high scar burden (see fig 2.4), Plein et al(98) were able to demonstrate that it is possible to accurately measure the extent of ischaemia in the presence of scar. Significantly different ischaemia: scar burden ratios were measured in patients with NSTEMI and those with STEMI. The ratio of scar to ischaemia was 3.5, 1.0 and 0.2 for Q-STEMI, Non-Q STEMI and NSTEMI, respectively.

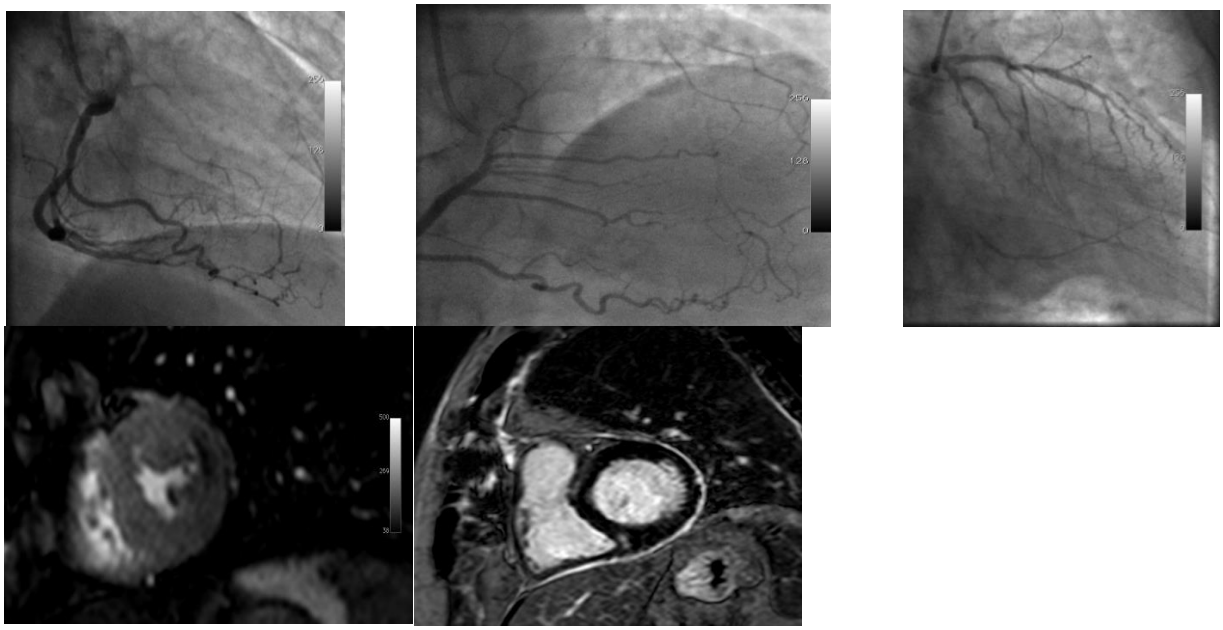


Fig 2.4: Angiographic images showing an occluded circumflex artery well collateralised from the RCA. Corresponding CMR images show a lateral perfusion defect that is consistent with the area of myocardial scarring demonstrated on the late gadolinium enhancement views. The perfusion defect does not extend beyond the area of scar suggesting that there in no peri-infarct ischaemia

2.3.2 FFR IN MYOCARDIAL INFARCTION

There is a general consensus that in the acute phase of myocardial infarction (MI), FFR is neither reliable nor useful to assess the culprit lesions and should be deferred until after stabilisation. The main concern is that of raised microvascular resistance as a consequence of microvascular injury due to thromboemboli, platelet plugging, coronary vasospasm and endothelial dysfunction.

There have been a number of studies testing the utility of FFR in the early days after acute myocardial infarction. Samady et al in one study (58), performed FFR measurements in patients in the infarct related artery early in the days after NSTEMI and STEMI and subsequently did myocardial contrast echocardiography (MCE) and single photon emission computed tomography (SPECT). They demonstrated that early into the infarct, an FFR of <0.75 reliably identified the presence of reversible ischaemia.

De Bruyne et al (57) obtained FFR measurements and SPECT studies before and after PCI in 57 patients 3.7 +/- 1.3 days after infarction also in the infarct related artery. To identify true reversibility, follow-up SPECT was performed 11 weeks after PCI. The sensitivity, specificity, and concordance of FFR ≤ 0.75 for detecting true reversibility on SPECT were 88%, 93%, and 91% (chi-square $p < 0.001$) and for detecting reversibility on myocardial contrast echo were 90%, 100%, and 93% (chi-square $p < 0.001$), respectively. The optimal FFR value for discriminating inducible ischaemia on non-invasive imaging was also 0.78, similar to findings by Samady et al (58). They concluded that that the 0.75 cut-off value of FFR to distinguish patients with positive from patients with negative SPECT imaging is valid after a myocardial infarction and that for a similar degree of stenosis, the value of FFR depends on the mass of viable myocardium. The diagnostic accuracy demonstrated in this study is commendable but correlating an FFR value done early in the days after infarction with a non-invasive imaging test done 11 weeks later does raise questions regarding the validity of the findings. In another study, McCLish et al (99) demonstrated that for angiographic lesions of matched lumen diameter and lesion length, FFR of vessels supplying recently infarcted myocardium is similar to FFR in non-infarcted myocardium in a control population. Additionally, the correlation between percent diameter stenosis and FFR and the slope of correlation is similar in recently infarcted and non-infarcted myocardium. This study was done 1 to 5 days after myocardial infarction and suggests that recent infarction and its accompanying microvascular injury may not significantly alter FFR measurements. However, the study is limited by the

lack of visualisation of and correction for the extent of infarction. In addition, there was a significant difference in LV function between the two groups, which, may impact on differences in flow within the coronary arteries, and subsequent FFR results. Overall though, FFR assessment has been demonstrated to be a feasible method of assessment in the days after infarction.

During the first few days after coronary occlusion, infarct volume can almost double, because of the addition of oedema and myocardial death. Subsequently, infarct volume may shrink to 25% of its initial volume as necrotic muscle is replaced by scar over 4 to 6 weeks. The reduction in the total mass of functional myocardium supplied by a given stenosis in an infarct related artery will tend to decrease(57) and therefore, by definition, hyperaemic flow and thus hyperaemic gradient will both decrease as well and consequently FFR increases. It is argued that this does not mean that FFR underestimates lesion severity after myocardial infarction; it just reflects that the visual assessment of a stenotic segment does not necessarily reflect its functional importance. This principle is illustrated in Fig 2.5.

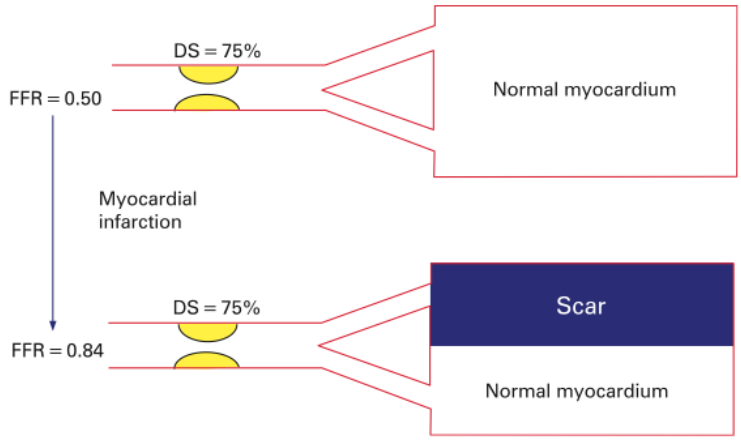


Fig 2.5: Schematic diagram demonstrating the FFR result in patients with myocardial scarring (Adapted from (57))

Thus, the mass of viable myocardium and also the microvascular resistance in the infarcted territory can affect the FFR.

There has been conflicting data regarding the presence or absence of microvascular dysfunction in areas remote from the infarcted territory, with earlier studies suggesting that microvascular function would be abnormal in remote regions (100, 101). Recent data,

however, suggests that the hyperaemic myocardial resistance in viable myocardium even within the infarcted area remains normal (100). This study aimed to assess whether microvascular resistance in the infarct area is different from that in the reference area in patients with chronic myocardial infarction. In patients with chronic MI and a reduced ejection fraction, a good correlation was found between FFR measurements in the infarct related artery and RFR (the relative flow reserve) which is the ratio of myocardial blood flow in the stenotic area to blood flow in a normally perfused reference area, at maximal hyperaemia. The mean FFR and RFR values were 0.75 ± 0.16 and 0.74 ± 0.18, respectively. A significant correlation ($r = 0.81$; $P < 0.0001$) was found between FFR and RFR. The authors concluded that microvascular resistance in the viable myocardium does not differ from that in the reference area.

Thus, the data regarding the presence of raised microvascular resistance in patients with chronic myocardial infarction is not clear-cut and there is little direct evidence on the correlation and accuracy of FFR measurement within the context of chronic myocardial scar. Despite these limitations, the application of the established FFR cut-off value in the setting of partially infarcted territories appears to be accepted.

2.4 SERIAL STENOSIS / DIFFUSE DISEASE

With increasingly complex percutaneous interventional procedures being performed, the assessment of diffuse disease and serial stenoses also becomes important. For accurate FFR measurement interpretation an understanding of the mechanisms of pressure measurement is required so that the results may be interpreted correctly.

As CMR assesses blood flow through the myocardium, the complexity of coronary disease is largely irrelevant to the interpretation of the presence of myocardial ischaemia.

2.4.1 CMR IN SEQUENTIAL STENOSIS AND DIFFUSE DISEASE

In the subgroup of patients, where the FFR measurement may be overestimated thus underestimating the severity of disease, CMR perfusion imaging is at an advantage as it does

not measure lesion or vessel severity. It assesses the impact on myocardial blood flow of the vessel as a whole.

2.4.2 FFR IN THE ASSESSMENT OF SERIAL STENOSIS AND DIFFUSE DISEASE

It is well recognised that atherosclerosis is diffuse in nature and the presence of diffuse disease is often associated with a progressive decrease in coronary pressure and flow or may manifest as a series of stenosis. The assessment of serial lesions and diffuse disease invasively by FFR is complex.

Practically, in these cases the measurement of FFR involves the pressure wire being pulled back steadily from the distal to proximal vessel segment during continuous hyperaemia induced by intravenous adenosine. In the presence of a focal narrowing, there will be an abrupt change in distal pressure, whereas in diffuse disease there will a gradual increase.

However, the very nature of diffuse disease means that even if the FFR reduces across an artery, there is no focal narrowing to stent. To an untrained eye, it may seem that angiographically there is no significant disease. Such diffuse disease and its haemodynamic impact should always be kept in mind when performing functional measurements.

In patients with diffuse disease with no focal stenosis, chest pain is often considered non-coronary because no single focal stenosis is found, and the myocardial perfusion imaging is wrongly considered false positive. Both angiographic assessment and FFR measurement will be misleading in these circumstances.

When several stenoses are present in the same artery, it is important to realise in such cases that each of several stenoses will influence hyperaemic blood flow and therefore FFR across the other one. When a second stenosis is present along the same epicardial vessel, flow through one stenosis will be submaximal because of the second stenosis, even during vasodilation of the microvasculature. It is, however, possible to assess the FFR value and the initial validation work for these measurements was undertaken in 5 dogs with 2 stenoses of varying severity(101).The influence of the distal lesion on the proximal was found to be more important than the reverse. For 2 stenoses in series without intervening arterial branches the equation of FFR remains valid for determining the haemodynamic

consequences of both stenosis together. However, in the case of a normal side branch between sequential stenosis, diverting flow to the normal low-resistance branch during hyperaemia could reduce flow through the distal stenosis. This phenomenon is called branch steal and its quantification requires pressure and flow measurement or quantitative angiographic analysis of the entire coronary tree.

After the initial animal validation work, these measurements were further validated in a human study also with 32 patients who had at least 2 serial stenosis in one coronary artery (102). Relevant pressures were measured before the intervention, after the treatment of one stenosis, and after the treatment of both stenoses, the true FFR of each stenosis (FFR_{true}) was directly measured after the elimination of the other stenosis and compared with the value predicted (FFR_{pred}) from the initial pressure measurements before treatment. FFR_{pred} was close to FFR_{true} in all patients (0.78±0.12 versus 0.78±0.11 mm Hg; r=0.92). The authors do concede, however, that one stenosis influences the haemodynamic effects of another in a sequence that may result in a mutual underestimation of the severity of each unless stenosis interaction is accounted for. The overestimation of FFR is more pronounced for the proximal lesion than for the distal lesion.

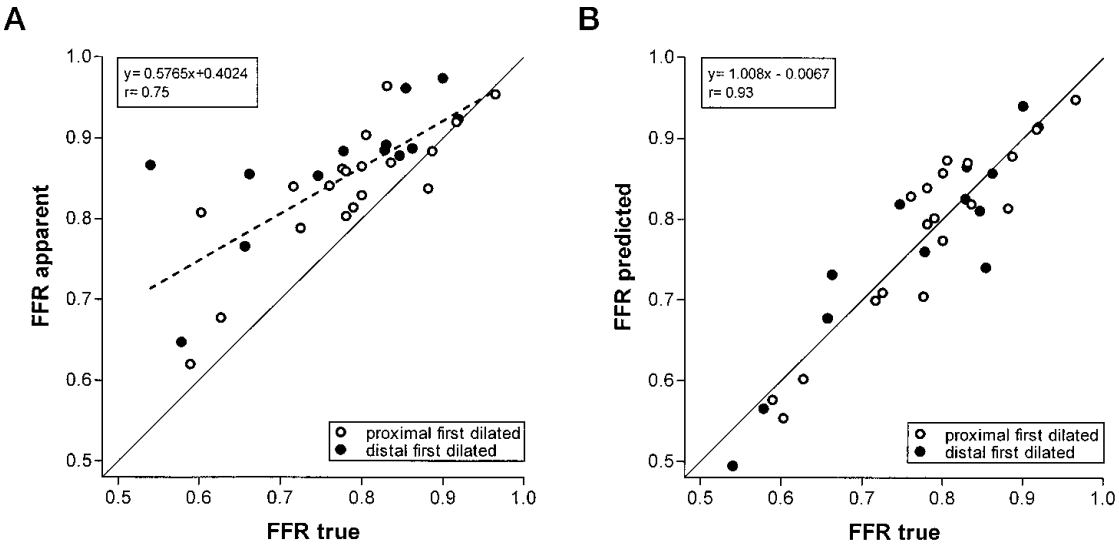


Figure 2.6. Influence of the presence of 1 stenosis within a coronary artery on the haemodynamic effect of the other. The clear dot indicates patients in whom the proximal

stenosis was treated first; the solid dot, patients in whom the distal stenosis was treated first. A, with increasing severity of 1 stenosis, the underestimation of the haemodynamic severity of the other stenosis becomes more pronounced. The solid line is the line of identity, and the dashed line, the regression line for measured data. In B, the regression line almost coincides with the line of identity (and therefore is not visible).

When calculating the FFR of each stenosis separately, a different equation needs to be used, requiring the pressure between both the stenoses to be measured separately. Realistically, however, the measurement of FFR between two stenoses is neither practical nor easy to perform and therefore not done routinely. Additionally to calculate the true FFR a wedge pressure also needs to be measured which adds to the complexity of the procedure.

When faced with the scenario of sequential stenosis in the catheterisation laboratory, consideration needs to be given to the fact that this may lead to overestimation of FFR or underestimation of stenosis severity. It is important to realise that one stenosis influences the haemodynamic effects of another in a sequence that may result in an underestimation of the severity of each unless stenosis interaction is accounted for.

A recently published paper by Yong et al (103) assessed the impact of a downstream stenosis on left main FFR assessment. In this study, variable stenoses were created in the left main arteries and downstream epicardial vessels in 6 anaesthetised male sheep using balloon catheters. A total of 220 pairs of FFR assessments of the left main stenosis were obtained, before and after the creation of a stenosis in a downstream epicardial vessel, by having a pressure wire sensor in the other non-stenosed downstream vessel. They found that the apparent left main FFR in the presence of a stenosis was significantly higher compared with the true FFR in the absence of downstream stenosis. (FFRtrue; 0.80±0.05 versus 0.76±0.05; estimate of the mean difference, 0.035; $P<0.001$). In all lesions where there was a difference, the epicardial lesion was in the proximal part of the stenosed vessel and the epicardial FFR (combined FFR of the left main and downstream stenosed vessel) was <0.50. It appears therefore that there is a clinically relevant effect on the FFR of the left main stem on the presence of a tight and proximal epicardial stenosis.

2.5 COLLATERALISATION AND CHRONIC TOTAL OCCLUSIONS

Increasingly, there is interest in opening up chronic total occlusions percutaneously due to improved equipment and success rates. A recent meta- analysis (104) has documented benefits specific to successful chronic total occlusion (CTO) PCI with respect to improvement in symptoms, reduction in ischaemia, and even a suggestion of better outcomes. For CTO's the correct interpretation of ischaemia and viability to guide revascularisation is more important due the complex nature of the procedure and the increased associated risks of complications.

2.5.1 CMR AND CHRONIC TOTAL OCCLUSIONS

In patients with CTO's, the main use of CMR has been to identify areas of viability or ischaemia in the territory to see if any benefit from revascularisation is likely to be derived. In CTO's the evidence for revascularisation is less robust than for stable angina and therefore ESC (2) guidelines recommend ischaemia directed revascularisation.

Frequently, the presence of collaterals leads to a decision enforcing optimal medical therapy regardless of the presence of ischaemia. However, there is little data assessing the diagnostic accuracy of CMR perfusion imaging in CTO's, and the potential discordance with invasive assessment especially in the presence of collaterals need to be understood in order to pursue the right management strategy.

Patients with CTO's have been studied previously by Aboul-Enein et al (105) who investigated the Rentrop angiographic grading of collaterals and myocardial perfusion imaging by SPECT, in patients with single vessel CTO's and no prior infarction. The stress induced perfusion defects did not differ between the groups with good or with poorly developed collaterals. However, there was a difference in resting perfusion suggesting that there may be some protective effects of collateralisation.

Wright et al (106) retrospectively compared the association between ischaemia and myocardial perfusion imaging and the presence of collaterals on angiography with hard

cardiac events in 21 patients with CTO's treated medically over a mean follow up of 23 months. They also demonstrated that the presence of collateralisation did not predict either ischaemia or hard cardiac events.

Meuhling et al (107) performed CMR perfusion imaging in 30 patients with one occluded artery and no other flow limiting stenosis to assess the transmural extent of infarction, perfusion during rest and adenosine induced hyperaemia, and regional wall thickening in both collaterally dependent and antegradely perfused grade (0-3). They found that in 15 patients with < 50 % LGE, perfusion was similar in antegradely and collateral dependent myocardium.

In patients with greater than 50% LGE, perfusion was lower in collateral dependent than antegradely perfused myocardium, essentially demonstrating that in patients with scar, there is more contribution from antegrade perfusion than from collateral perfusion.

From these small studies, it is difficult to come to any robust conclusion about the extent and effects of collateralisation on the assessment of ischaemia.

2.5.2 FFR AND CHRONIC TOTAL OCCLUSIONS

The utility of FFR in patients with a CTO is limited as it is not technically feasible to pass a pressure wire through an occluded artery. However, it is still possible to assess the remaining arteries with FFR and also to assess the extent of collateralisation in different grades of stenoses.

The concept of FFR can be extended to calculate separately myocardial, coronary, and collateral perfusion and it is possible to distinguish separately the contribution of coronary blood flow and collateral blood flow to myocardial blood flow (FFR_{myo} is the maximum myocardial blood flow being maintained and equals $FFR_{Coronary}$ and $FFR_{Collaterals}$). The FFR of the collaterals is also known as the collateral flow index (CFI). Recruitable collaterals can be assessed at coronary artery occlusion by the simultaneous measurement of mean arterial, coronary wedge and central venous pressure. CFI can be calculated as *FFR coll = (Pw –Pv)/ (Pa-Pv)*

Both pressure derived and doppler derived CFI's have been clinically validated. Pressure derived CFI was shown to have an excellent correlation with the extent and severity of a 99Tc-sestamibi defect in the territory of an occluded artery during balloon angioplasty in the catheterisation laboratory (108). Doppler derived CFI has been shown to have excellent correlation with pressure derived CFI, and low values for both indexes were found to be highly predictive of ischaemic ST segment changes on electrocardiography during balloon occlusion.

The study by Matsuo et al (108) showed that a close correlation is present between collateral fractional flow reserve, calculated from coronary pressure measurements, and the extent and severity of hypoperfusion of the territory supplied by the occluded artery in relation to normally perfused myocardium. 24 consecutive patients with stable angina and single LAD stenosis underwent simultaneous measurement of aortic pressure, coronary wedge pressure, and pressure during balloon inflation. They found that the pressure-derived collateral indexes (Pw, Pw/Pa, and FFR_{coll}) ranged widely but were closely correlated with the extent and severity scores of the nuclear occlusion images. Of all parameters, FFR_{coll} correlated best with the severity score at imaging (r = -0.88).

Werner et al (109) demonstrate that in patients with a CTO, angiographically well-developed collaterals do not provide a sufficient functional supply to the occluded arterial segment. 107 patients with a CTO and no prior myocardial infarction had invasive assessment of collateral function. Intracoronary doppler flow velocity and pressure recordings were obtained distal to the occlusion before the first balloon inflation and collateral function indices were calculated. Even in patients with normal regional LV function, collaterals provide a normal coronary flow reserve in less than 10%. Only 7% of patients had an increase in collateral flow reserve >2.0 during pharmacological stress, whereas coronary steal occurred in one third independent of regional LV function. The high prevalence of coronary steal in CTO's indicates that patients with even well collateralised CTO's may benefit from revascularisation. This suggests that there may be significant ischaemia even in the presence of a good collateral circulation.

The donor artery that is supplying the collaterals to the occluded artery can also be assessed by FFR but assessing and taking into account the extent of collateralisation is important. When providing collaterals to another territory, the size of the myocardial bed inevitably

increases. Therefore distal pressure will be low resulting in a larger pressure drop across a given stenosis. FFR measurement across the same stenosis would result in a lower pressure drop if the myocardial bed were smaller, i.e. in the absence of collaterals. There are reports in the literature, which support this phenomenon but this area has not been formally studied (110, 111).

The FFR measurement is thought to be appropriate as it "corrects" for the size of the myocardial bed being supplied, as a larger myocardial area means that the benefit to be achieved from PCI would be greater than that of just a smaller territory. Although this may lead to an angiographic- functional mismatch with an angiographically mild stenosis having a significant FFR result, physiologically the stenosis is deemed significant. This should theoretically cause a perfusion defect in the area supplied by the donor artery, as this is the area whereby the "coronary steal" is occurring.

If the stenosis of the artery being collateralised is relieved, the myocardial bed of the donor artery will reduce, resulting in an increase in the FFR result.

This observation was demonstrated in a study by Leone et al(112) aiming to evaluate the influence of the amount of myocardium subtended by a stenosis on the FFR value. They studied 213 intermediate stenosis, in 184 patients and matched them with stenosis of similar type. The extent of myocardium was allocated according to jeopardy scores. They found that the stenosis that subtended a larger extent of myocardium had more significant FFR values. Interestingly, they also found that in the subanalysis of a proximal LAD lesion, the presence of a concomitant well-collateralised CTO is indeed associated with a significantly lower FFR. Taken together, these data suggest the importance of the functional assessment of stenoses in particular when located in proximal LAD, in the presence of collateralised CTO or in general when a large amount of myocardium is subtended by the index stenosis. However, this study was limited by the lack of imaging data to support the extent of ischaemic myocardium, using indirect measures via jeopardy scoring instead.

2.6 SUMMARY

From the literature, it appears that the measurement and interpretation of FFR and also of CMR images is not straightforward in patients with complex disease. It does lead one to question the applicability of much of the validation work that was carried out in patients with single vessel disease.

It is unclear whether increased microvascular resistance leads to abnormal perfusion detected by CMR perfusion imaging. FFR may also underestimate the severity of a stenosis in patients with complex coronary disease, due to the concomitant presence but neglect of abnormalities in microvascular resistance.

In multivessel disease, the evidence suggests that FFR does differentiate physiologically important lesions compared to invasive angiography. It remains to be seen whether a strategy of targeted revascularisation to the lesions causing most ischaemia is beneficial in terms of symptomatic improvement and prognostic benefit. The utility of CMR perfusion imaging to accurately guide decision-making in multi-vessel disease still needs to be assessed.

With the potential of CMR scanning to assess scar size and the presence of ischaemia, an assessment of the correlation of the presence and extent of peri-infarct ischaemia with the FFR result is possible.

In diffuse disease, a “step” in the FFR measurement may not be evident and this may suggest that there is no flow-limiting lesion. However, the overall impact of luminal reduction will be an impairment of flow that should manifest as a perfusion defect on CMR imaging. Similarly, the assessment of a stenosis in sequence may result in overestimation of FFR in the presence of a perfusion defect.

Understanding the limitations of both techniques is important for the appropriate use of these valuable tools, especially in the setting of more complex coronary and myocardial disease.

CHAPTER 3: GENERAL METHODS – THE MR INFORM STUDY

Some of the patients used in the comparative studies between FFR and CMR were recruited to take part in the MR-INFORM clinical trial.

(ClinicalTrials.gov Identifier:NCT01236807)

This is an international randomised controlled trial of FFR vs. CMR to guide the management of patients with coronary artery disease and is still currently recruiting.

Currently there are over 600 patients recruited to this study, which aims to recruit 918 patients.

Analysis of subgroups where there is discordance between the two tests is part of the exploratory endpoints of the main trial. One of the disadvantages of using these patients is that the power calculations are based on the primary endpoint of the main clinical trial. However, these patients are a particularly interesting sub group as they have had both an invasive and non-invasive assessment of ischaemia. In addition, some patients were recruited from a second site, Porto in Portugal under the direction of Dr Nuno Bettencourt.

In this chapter I will describe the general methods of the main MR-INFORM trial. My involvement in this study was writing the protocol, finalising the trial design including all important decisions on the nature of the trial, definition of end points, statistical power etc. Furthermore, I proceeded to get regulatory approval for the study, and set up enough sites to ensure adequate recruitment both nationally and internationally. Additionally, I recruited patients from our site and was responsible for the CMR scanning and follow up of these patients.

The following chapter is adapted from the following publication:

Hussain ST, Paul M, Plein S, McCann GP, Shah AM, Marber MS, et al. Design and rationale of the MR-INFORM study: stress perfusion cardiovascular magnetic resonance imaging to guide the management of patients with stable coronary artery disease. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance. 2012;14:65(113)

3.1 BACKGROUND AND RATIONALE FOR STUDY

Over the last few years, there have been a number of landmark trials questioning previously accepted management strategies for patients with stable coronary artery disease. The COURAGE(67) trial has shown no benefit of routine revascularisation both in terms of prognosis and long term symptom relief in patients with stable angina. However, subgroup analysis of the COURAGE data(68), suggests that the prognosis of patients receiving optimal medical therapy (OMT) alone or percutaneous coronary intervention (PCI) and OMT is correlated to their ischaemic burden and the amount of ischaemia reduction achieved by therapy, as assessed by SPECT. The assessment of prognosis, however, was exploratory, and not associated with outcome when adjusted for treatment.

There is evidence that the presence of stress-induced myocardial perfusion defects identified by non-invasive imaging tests such as SPECT have prognostic significance(114). An observational study of 10 627 patients with stable angina and evidence of ischaemia as measured by SPECT described a survival advantage for revascularisation (of which 52% was PCI) over medical therapy in patients with ischaemia of more than 10% of the myocardium (66). An alternative approach is the use of invasive FFR measurements to assess the functional significance of coronary stenoses. The FAME(115) and DEFER(27) trials have demonstrated that patients in whom angioplasty is only performed on FFR positive stenoses have an improved outcome compared to those patients in whom the revascularisation decision is based on a visual estimate of angiographic severity alone. The 2-year follow-up of the FAME patients showed a significant reduction in major cardiac events (MACE) in patients guided by FFR. Thus, there is accumulating evidence dictating a shift away from a purely anatomical assessment for coronary artery disease to a functional assessment. These data are of specific importance as most studies so far have determined diagnostic accuracy, whereas FAME and DEFER are among the few studies, where different diagnostic strategies were used to guide further management and thus improve outcome.

CMR perfusion is a well-established, non-invasive test with excellent accuracy for the detection of coronary artery stenosis(18) as well as abnormal FFR (31, 63). Multicentre data

has demonstrated non-inferiority of CMR myocardial perfusion imaging in comparison to SPECT for the assessment of myocardial ischaemia (15). In a recent single centre study of 750 patients the superiority of CMR perfusion in comparison to SPECT was shown mainly due to improved sensitivity (86.1% vs 65.5%) (5). In addition, patients with a negative perfusion scan have a low likelihood (<1%) of a major cardiac event over the following two years (10) (116) (117). Thus, CMR perfusion seems well suited to guide the management of patients with stable coronary artery disease similar to invasive FFR measurements(1).

Although treatment decisions are increasingly being based on the combination of symptoms and objective proof of ischaemia, there is insufficient evidence on the best management strategy for patients with stable angina(118) and comparative effectiveness. The aim of the MR-INFORM study, therefore, is to establish whether guiding the management of patients with a moderate to high risk of coronary artery disease by CMR perfusion is non-inferior to guiding the management of these patients by invasive angiography and FFR.

3.2 STUDY DESIGN

3.2.1 HYPOTHESIS

The principal hypothesis is that selecting patients with stable angina for revascularisation and optimal medical therapy (OMT) or OMT alone based on CMR myocardial perfusion is non-inferior to selecting patients based on routine coronary angiography and fractional flow reserve (FFR) in terms of subsequent major adverse cardiac events.

3.2.2 STUDY CONDUCT AND RANDOMISATION

MR-INFORM is a multi-centre, randomised controlled, non-inferiority trial. It is actively recruiting within the UK, Germany, Portugal and Australia. The study is performed in accordance with the principles of the Declaration of Helsinki; with all patients providing informed written consent prior to testing. The study protocol and other relevant documentation have been approved by the South London Ethics Committee (UK) and the relevant national ethics committees as well as registered on ClinicalTrials.gov identifier: NCT01236807:

(http://clinicaltrials.gov/ct2/show/NCT01236807?term=MR+INFORM&rank=1). Suitable patients are identified in the outpatient clinics and from the angiography and CMR waiting lists of the recruiting centres. If they meet the inclusion criteria and none of the exclusion criteria and provide written informed consent, they are enrolled into the study.

Patients are electronically randomised prior to the baseline CMR scan via a web-based randomisation service into randomly varying block sizes of 2 and 4, stratified by study site and gender with an allocation ratio 1:1 to MR-INFORMED or FFR- INFORMED.

3.2.3 FFR INFORMED GROUP

Within the FFR-INFORMED group, the baseline CMR scan is blinded. This scan is not used to guide further management but will provide valuable additional scientific data that will be used in analyses specific to the sub studies (described below). All patients in this group are examined with invasive angiography, FFR is performed in all arteries >2.5 mm with a diameter stenosis >40%. FFR is attempted in all arteries up to a 99% stenosis, as long as patency is not compromised. Although this strategy differs from clinical practice which tends to focus more on intermediate lesions, evidence from the FAME trial suggests that even in severe and mild stenosis the visual estimate can be inaccurate (29).

The results of invasive angiography and the FFR result are used to guide further treatment. Any narrowing with an FFR of >0.8 is regarded as not haemodynamically significant, whereas a narrowing with an FFR of ≤0.8 or a total occlusion is regarded as significant and revascularisation is indicated. The decision on the mode of revascularisation is left to the treating cardiologist and depends on local practice. In the case of repeat revascularisation, when symptoms are on-going, revascularisation will be guided according to either the FFR or CMR results depending on the group randomised.

3.2.4 MR INFORMED GROUP

Within the MR INFORMED group, further management is dictated by the results of the baseline CMR scan. A visual assessment of the significance of ischaemia and the territories involved is made (see investigation reporting below). Patients with significant perfusion defects are referred for angiography and revascularisation is guided by the ischaemic

territories identified on the CMR scan in combination with the results of the angiogram. FFR should not be done in this group. See Fig 3.1 for study design.

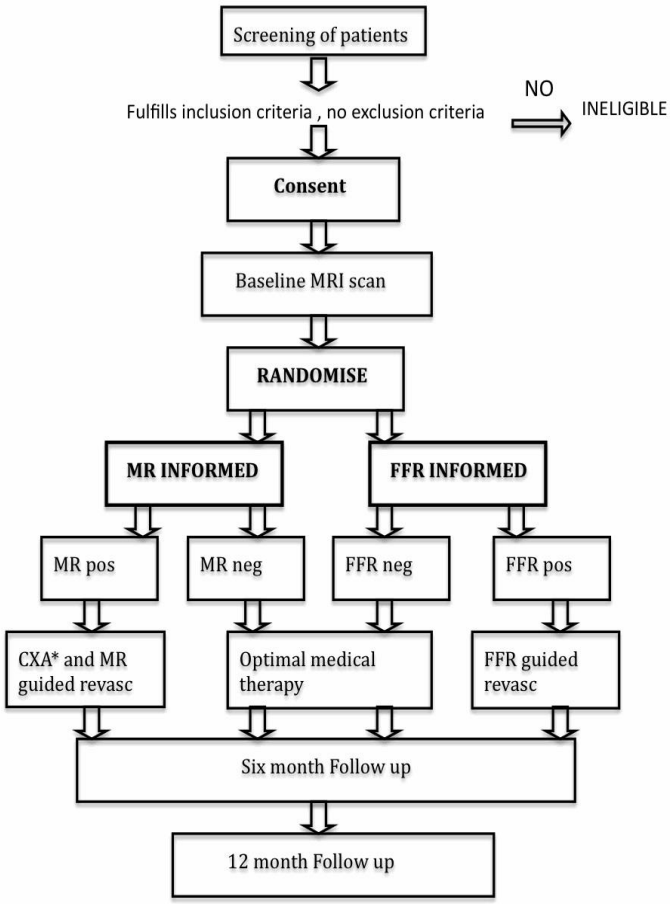


Fig 3.1: Study Flow diagram outlining the study design. *CXA = Coronary Angiography.

3.2.5 PATIENT RECRUITMENT, INCLUSION AND EXCLUSION CRITERIA

Patient Population

Patients recruited into the study have typical symptoms of angina (Canadian Class Symptoms CCS 2-3), and either a positive exercise/bicycle test or more than two cardiovascular risk factors. Exclusion criteria include contra-indications to CMR imaging or to adenosine, poor renal function (eGFR<30), LVEF <30%, PCI within the last 6 months, and previous Coronary artery bypass grafting (CABG). A prior myocardial infarction is not an exclusion criterion. The complete inclusion and exclusion criteria are listed in table 3.1**.**

Table 3.1: Inclusion and Exclusion criteria

Inclusion criteria	**Exclusion criteria**
CCS Class 2 and 3 *AND EITHER:* 2 or more of the following risk factors (diabetes, hypertension, smoking, family history, hypercholesterolaemia) *OR* Positive Exercise treadmill/bicycle test	Contra-indications to CMR
	Contra-indications to adenosine (AV-block 2 or 3, symptomatic bradycardia, COPD with evidence of bronchospasm or asthma)
	Cardiac arrhythmias which may compromise image quality, atrial fibrillation or frequent ectopic beats >20bpm)
Age >18 yrs	Known Left ventricular ejection fraction of less than 30 %
Willing to undergo all study procedures	Persistent CCS class 4 angina
	NYHA class 3 and 4
	Previous coronary artery bypass grafts
	PCI within the previous 6 months
	Poor renal function (GFR<30ml/min) and /or allergy to contrast media
	Inability to lie supine for 60 mins
	Unstable medically
	Participating in any other clinical trial
	Pregnancy / breast feeding

All patients have a baseline stress perfusion CMR scan and further management will depend on whether they have been randomised to the MR-INFORMED or the FFR-INFORMED arm of the trial. In addition, all patients receive optimal medical therapy.

3.3 ANALYSIS AND INTERPRETATION OF RESULTS

3.3.1 CMR IMAGING

CMR imaging is performed on 1.5T scanners (various vendors); total scan duration is approximately one hour. See Figure 3.2. All images are acquired using phased array surface coils during mild expiration and electrocardiographic triggering. Cine images are acquired in the 4-, 3-, 2-chamber and contiguous short axis views using a steady state free precession (SSFP) sequence. For perfusion, a basal, midventricular, and apical short axis slice will be acquired during the first pass of 0.075ml/kg of a 1-molar gadolinium based contrast agent injected with a power injector at a flow rate of 4mls/s. The exact details of the sequence varies between different scanners used but will fulfil certain basic criteria, including high spatial resolution (< 3mm x 3mm), acquisition duration <180ms per slice, 90° saturation pre-pulse, fixed pre-pulse delay and dual bolus contrast injection allowing semi-quantitative and fully quantitative analysis(119). Hyperaemia is achieved by infusion of adenosine at 140mcg/kg/min for 3-4 minutes. If there is neither a heart rate increase >10bpm nor a systolic blood pressure drop >10 mmHg from baseline nor symptoms the adenosine dose will be increased to 170mcg/kg/min after 2 minutes and to a maximum dose of 210mcg/kg/min(120). All patients are asked to avoid caffeine, but to continue with their normal medication for 12 hours prior to the scan. For the perfusion measurements, contrast agent will be injected at the third minute of adequate adenosine stress using a dual bolus method. A dose of 0.075 mmol/kg of a 1-molar gadolinium-chelate (Gadobutrol, Gadovist®, Bayer, Germany) is injected for the main bolus preceded by the same volume of a 10% diluted contrast agent dose for a prebolus both flushed with 25ml of saline. Rest perfusion imaging is performed 10 min after stress perfusion to allow for clearance of most of the contrast agent.

Late enhancement imaging is then carried out using an inversion recovery turbo gradient echo sequence.

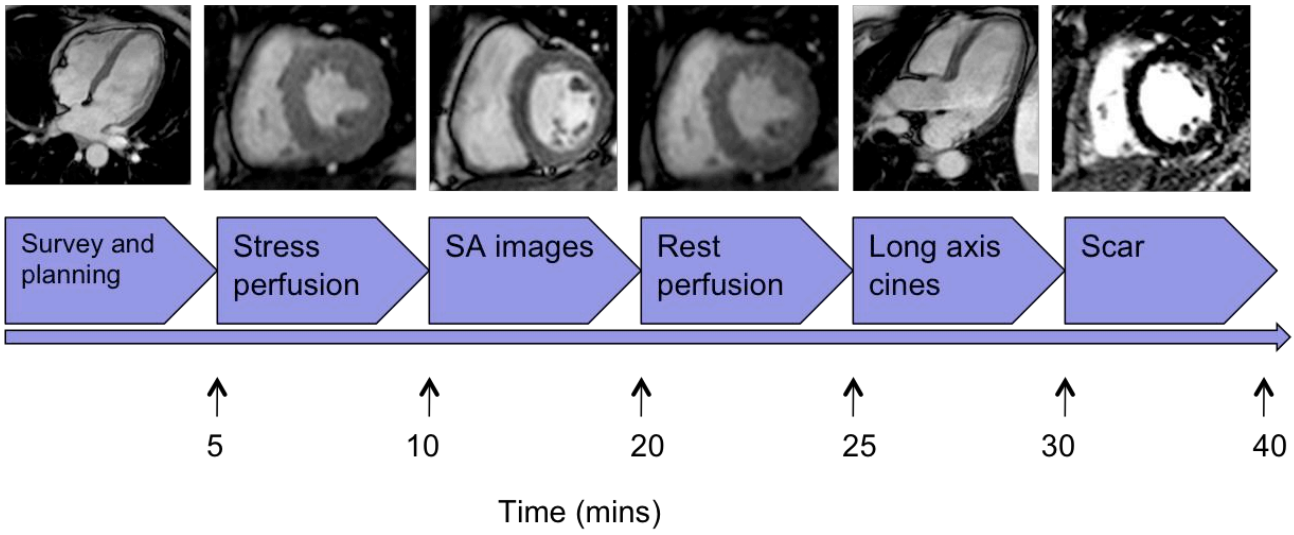


Fig 3.2: MR-INFORM cardiac magnetic resonance protocol.

After individual patient planning using survey scans, intravenous adenosine is given according to the protocol. First pass stress perfusion imaging is done during stress visualising the first passage of a 0.75 mmol/kg contrast agent bolus through the myocardium. Short axis (SA) cine images are acquired. Rest perfusion images are acquired during an injection of a second bolus of 0.75mmol/kg contrast agent. 10 minutes after an additional injection of 0.05 mmol/kg of contrast agent to increase the total dose of contrast agent to 0.2 mmol/kg. A modified Look-Locker inversion time scout is performed prior to late gadolinium enhancement imaging in short axis and long axis views. During the wait time after the last contrast agent injection long axis images in the 4 chamber, 3 chamber and the 2 chamber views are obtained.

3.3.2 FFR MEASUREMENT

In the FFR-INFORMED arm of the trial, all patients will have coronary angiography and FFR measurement as required.

At angiography, any arteries with a diameter of >2.5mm and a diameter stenosis between 40–99% will be assessed with FFR. A 0.014 guidewire (Radiwire, St. Jude Medical, St. Paul, MN, USA or Volcano, Volcano Corporation, San Diego, CA) will be introduced, calibrated and advanced into the coronary artery distal to the stenosis. An intravenous adenosine infusion (140mcg/kg/min) will be used to induce maximal hyperaemia. FFR is calculated as the ratio of

the mean distal coronary pressure measured by the guide-wire to mean aortic pressure measured by the guiding catheter. Revascularisation will be recommended in the FFR group if FFR is <0.80. In the case of a chronic total occlusion, FFR is regarded as positive and a default value of 0.5 is assigned to the chronically occluded vessel. In the case of triple vessel disease, an attempt should be made to do FFR in all three arteries.

If there is more than one artery that needs to be revascularised, the PCI procedure can be staged. If this occurs, follow-up will begin after the first procedure, and the endpoints will include both procedures.

Post-interventional FFR is useful but not mandated in order to keep the procedure as simple as possible.

3.3.3 CMR ANALYSIS

The local supervising CMR physician as per normal clinical practice will do the CMR analysis for the MR-INFORMED group.

The following data are collected:

1) Image quality (assessed on a grade of 1 to 4 – poor to excellent)

2) Presence of scar tissue and transmurality (1=1-25%; 2=25-50%; 3=51-75%; 4=>75%) based on the AHA/ACC 17 segment model.

3) Perfusion analysis at stress and rest scored as significant, insignificant or no defect based on the AHA/ACC 16 segment model (see below).

4) Evidence of regional wall motion abnormalities (1=akinetic; 2=hypokinetic; 3=dyskinetic)

5) Quantitative analysis including end-diastolic and end-systolic volumes and ejection fraction

The baseline CMR scan in the FFR-INFORMED group will remain blinded.

3.3.4 PERFUSION ANALYSIS

The CMR perfusion images are interpreted visually and angiography recommended if the perfusion defect is classified as significant according to the presence of ischaemia in 2 segments of a 32-segment model (see below) i.e.:

- >60 degrees in either the basal or the midventricular slices or
- >90 degrees in the apical slice or
- Any transmural defect or
- A defect across two adjacent slices.

In the case of patients who have unexpected scar tissue evident on CMR, angiography will be recommended for all patients who have evidence of scar and peri-infarct ischaemia. When only scar is present, the management will be decided after an assessment of the transmurality of scar. In patients with transmural scar (>75%), and no additional ischaemia, angiography would not be recommended. In patients with partial transmurality (<75%) and no ischaemia, the need for angiography will be decided by the treating physician after an assessment of the patient's symptoms and risk. It is recommended, however, that the areas of ischaemia alone guide the subsequent revascularisation strategy.

3.3.5 RATIONALE FOR SIGNIFICANT ISCHAEMIA THRESHOLD

The rationale for the threshold at which ischaemia is deemed to be significant is based on data from Hachamovitch et al (66) who demonstrated that in patients with 10 – 12.5% ischaemic myocardium on SPECT, mortality is significantly higher if they are not revascularised in comparison to a revascularised group. The opposite is true in patients with less than 10% ischaemic myocardium.

With the high spatial resolution of CMR perfusion (< 3mm x 3 mm) it is possible to distinguish endocardial, non-transmural, perfusion defects from transmural (>75% wall thickness) perfusion defects. Thus, the myocardium can be divided into the 16 AHA/ACC segments with a subdivision into an endocardial and an epicardial half resulting in a total of 32 segments. Each of these segments represents approximately 3% of the myocardium; two positive

segments represent approximately 6%. Since there is no data available providing a direct comparison between the ischaemic burden in SPECT and CMR perfusion this level is used as a conservative threshold to refer patients to invasive angiography.

The criteria for interpretation of CMR scans, especially the differentiation between normal myocardium, non-transmural defects, and transmural defects, is discussed in detail with each site during the initiation visit using a set of example cases. In addition, CMR images will be periodically reviewed by the global coordinating investigator and selected coordinating investigators from participating countries who, in case of inconsistencies or differences in assessment, will contact the sites and consider specific training activities. Each site can invite a second opinion from the global coordinating investigator or a coordinating investigator from a participating country (or one of their experienced co-workers) in unclear cases.

3.4 OPTIMAL MEDICAL THERAPY AND FOLLOW UP VISITS

At baseline, 6 months and 12 months recommendations for therapy are made to the primary care physician in line with guidelines published by the Joint British Societies (121). See table 3.2 for the treatment targets.

Table 3.2: Risk factor goals

Risk factor Goals	
Blood Pressure	BP 130/80 mmHg
Diabetes Mellitus	Fasting or pre-prandial glucose of 4-6, or a HbA1C < 6.5%
Lipids	Total cholesterol less than 4mmol/l or an LDL <2.0mmol/l
Smoking	Smoking cessation
Weight	BMI<25

The goal of anti-hypertensive therapy is to achieve a blood pressure of less than 130/80 mmHg. The choice of anti-hypertensive therapy will be left to the treating physician. The aim of anti-lipid therapy is to achieve levels of LDL <2 mmol/l and total cholesterol <4 mmol/l. In the first instance, statin therapy will be initiated and then increased with the addition of a second agent if necessary. For patients with a BMI of > 25 kg/m^2, the primary health care physicians are asked to refer the patient for dietary advice. Similarly, smokers are referred to the smoking cessation clinic. Recommendations for referral and for the continuation of therapy are made to the primary health care physician.

In patients without diabetes, who have a raised random glucose, the primary health care physician is asked to repeat a fasting glucose to assess for sustained hyperglycaemia, in which case the appropriate dietary advice and/or diabetic treatment should be instituted. In the case of diabetics with a raised blood sugar, the primary health care physician is asked to measure HbA1c and to ensure that the patients' subsequent therapy is tailored to achieve a HbA1c of less than 6.5 mg/dl. All patients should be prescribed aspirin (clopidogrel if aspirin sensitive), statin therapy and an ACE Inhibitor (122).

3.4.1 CLINICAL FOLLOW UP

All patients undergo a thorough cardiovascular risk assessment at baseline with measurement of blood pressure, glucose levels, and body mass index, including measure of waist circumference, full lipid profile, the completion of a health questionnaire (EQ-5D) and a 12 lead ECG. CCS and NYHA class records symptomatic status. Medical therapy is optimised in all patients and the risk factor assessments are repeated at 6 and 12 months to assess the impact of medical therapy.

Furthermore, a 6 month follow-up CMR scan will be done in a subgroup of patients to assess for residual ischaemia, new scar formation and changes in left ventricular function and size after the initial therapy recommended after the baseline investigations. The result of this CMR scan remains blinded.

3.5 REVASCULARISATION

Revascularisation by either Percutaneous Coronary intervention (PCI) or coronary artery bypass grafting (CABG) will be guided by the ischaemic territories identified by either FFR or CMR perfusion, depending on the randomisation group. For example, if the CMR perfusion scan demonstrates a perfusion defect in the left anterior descending (LAD) territory and angiographically a narrowing is identified in the LAD and right coronary artery (RCA), only the LAD artery will be revascularised.

In visual triple vessel disease, the FFR or CMR results will be used to guide the decision towards CABG or PCI.

If there is more than one artery that needs to be revascularised, the PCI procedure can be staged. If this occurs, follow-up will begin after the first procedure, and the endpoints will include both procedures.

Post-interventional FFR is useful but not mandated in order to keep the procedure as simple as possible.

The specific revascularisation technique, i.e. type of stents used, staging of the procedure, PCI or CABG etc. will be decided by the treating interventionist and dictated by local guidelines. This is to reflect “real –world” practice and to acknowledge that practice varies between centres and countries. Similarly, the cardiac surgeons will decide on the type of surgical revascularisation that they will undertake.

In the case of patients who demonstrate scar and ischaemia on CMR perfusion subsequent revascularisation will be guided by areas of ischaemia alone rather than on the basis of scar.

See table 3.3 for examples of FFR guidance

Table 3.3: Examples of FFR guidance

Angiographic findings	**FFR result**	**FFR guidance**
LAD lesion 70% and RCA lesion 80%	LAD FFR 0.75 RCA FFR 0.85	PCI to LAD alone
CTO of LAD Circumflex(Cx) lesion 50 %	Assume LAD FFR 0.50 Cx FFR 0.70	Revasc of LAD and Cx
Diffuse disease in LAD	FFR < 0.80 on pullback	Operator can decide not to stent
Serial stenosis	FFR <0.80 beyond all narrowings	Stent most significant stenosis or one with the biggest pressure gradient
Angiographic 3VD	FFR <0.80 in 2 Vessels alone	2 Vessel revascularisation

3.6 RATIONALE FOR ENDPOINT SELECTION AND DEFINITION OF MACE

3.6.1 PRIMARY ENDPOINT

The primary endpoint is the occurrence of a Major Cardiac Event (MACE) at one year. This is a composite end-point of death, myocardial infarction, and repeat target vessel revascularisation. See table 3. 4 for detailed definitions of endpoints.

3.6.2 SECONDARY ENDPOINTS

- Symptoms (angina score, NYHA class) within 1 year
- Death, myocardial infarction and repeat revascularisation as individual components of MACE
- Cost-effectiveness of an MR vs FFR guided selection for revascularisation
- Occurrence of new myocardial scar tissue
- Ischaemia reduction in the FFR vs MR group after therapy

Table 3.4: Detailed definition of end-points

End Point		Definition
Death		All cause mortality
Myocardial Infarction	Spontaneous	Elevation of CK or Troponin above baseline with symptoms of ischaemia, ECG changes or imaging evidence of loss of myocardium(123)
	Peri-procedural	CKMB>3X ULN- upper limit of normal (post PCI 12-24hrs) CKMB>5X ULN (post CABG 24-72 hours) plus new Q waves or LBBB, new native vessel or graft occlusion, imaging evidence of loss of viable myocardium(123)
Repeat		Repeat PCI or CABG of the target

revascularisation		lesion performed for restenosis or other complication of the target lesion (from 5mm proximal to 5mm distal to the stent) (124)

3.6.3 ENDPOINT SELECTION

In a clinical trial, a primary endpoint is usually defined or specified as a measure that will be considered as the success of the therapy being tested. This can be a result, condition or event associated with individual study patients that is used to assess study treatments. The characteristics of endpoint measures are that they should be easy to diagnose, free of measurements error, internally and externally valid. Internal validity is demonstrated when the endpoint is directly linked to property of interest. External validity is demonstrated when an endpoint can be generalised to a wider population. They should also be clinically relevant. A trial might also define one or more secondary endpoints i.e. cost effectiveness, symptomatic improvement that will be measured and are expected to be met and also define exploratory endpoints that are less likely to be met.

The MR-INFORM trial has been designed as a non-inferiority trial with the primary endpoint defined as death, myocardial infarction or repeat revascularisation. Due to its non-inferiority design no difference between the two groups in reaching the endpoint is sought.

Although MR- INFORM is a combined imaging and interventional trial, it essentially assesses two investigative strategies that guide therapy and therefore adopts endpoints that are usually reserved for interventional trials. Interventional cardiology has a tradition of agreed upon clinical endpoint definitions and clinical trial methodologies (123, 124). This is to combat the variability in endpoint definitions that creates a barrier to the understanding of results across clinical trials or to the pooling of results. The endpoints used in MR-INFORM accurately reflect any improvement in survival by measuring death and myocardial infarction and also reflect the effectiveness of the revascularisation strategy by measuring repeat revascularisation. See table 3.5. All-cause mortality is the most unbiased method to report

deaths in a clinical trial or observational study, even though it may be less specific than deaths adjudicated as cardiac in origin.

Myocardial infarction during a clinical trial involving percutaneous intervention may occur during the immediate peri-procedural period as a result of the revascularisation procedure itself or long after the procedure as a result of spontaneous MI or late complication of the revascularisation procedure.

Recent guidelines provide a universal definition for clinical as well as investigational trial use (93). The global task force recommends the establishment of criteria based on troponin or creatine kinase Mb (CKMB) but notes the preference for troponin in all cases. For either troponin or CKMB, the upper range limit is defined as the 99th percentile of the normal range. The peri-procedural period includes the first 48 hours after PCI and first 72 hours after coronary artery bypass grafting (CABG).

Table 3.5: MR-INFORM endpoint characterisation.

Endpoint	Ease of diagnosis	No measurement error (reliable)	Internally valid	Externally valid	Clinically relevant
Death (All cause)	++++	++++	+	+++	++++
Myocardial infarction	+++	+++	+++	+++	++++
Repeat revascularisation	++	++	++++	++++	++++

3.6.4 DATA COLLECTION AND MONITORING

Patient demographic details, medical history and information on current medication use are collected. A 12 lead ECG will be performed at baseline and at 12 months. Blood tests will include a measurement of total cholesterol and full lipid profile, a random glucose measurement, and renal function (eGFR). These tests will be repeated at 6 and 12 months. A

full blood count will also be measured at baseline. Blood pressure, waist circumference measurement, and Body Mass Index will be determined at baseline, 6 and 12 months.

At the time of revascularisation (PCI or CABG), baseline troponin is measured. This will then be repeated 6 hours post PCI or 12 hours post CABG. If the troponin is raised, then a CKMB will be done at 12-24 hours post PCI or 36-72 hours post CABG. The definition of myocardial infarction is based on CKMB. See table 3.4 for detailed definitions of endpoints.

All study data is recorded via an electronic case report form (eCRF). Data is monitored at all sites for completeness and quality by the contract research organization (CRO). A full data-monitoring schedule is established and an independent data monitor will verify the eCRF against the source data.

Any adverse events or serious adverse events are recorded on the eCRF and forwarded to the sponsor and the CRO immediately. An independent Data Monitoring Committee reviews serious adverse events and any other trial safety issues.

3.7 SAMPLE SIZE AND STATISTICAL ANALYSIS

3.7.1 SAMPLE SIZE

The sample size calculation is based on the primary endpoint of death, MI, and repeat revascularisation at one year. A 10% event rate in the FFR group and an equivalence margin of 6% were assumed based on the results of the FAME study. (125) A sample size of 826 would be required to determine the non-inferiority of a CMR guided strategy compared to an FFR guided strategy with at least 80% power. Allowing for a dropout rate of 10% a total sample size of 918 patients is necessary. The calculation was carried out using STATA 11SE.

We do anticipate that there will be crossover between groups, most likely from the CMR group to the FFR group, when patients continue to experience symptoms and the CMR scan has been reported as negative. This will be taken into consideration during the statistical analysis which will be done on a per protocol and an intention to treat basis.

3.7.2 DATA ANALYSIS

Primary analysis

The main objective of this study is to assess whether an "MR-INFORMED" management strategy is non-inferior to an "FFR INFORMED" strategy for the clinical management of patients with angina who are at moderate to high risk of CAD. To satisfy this objective the study will test the following null-hypothesis

H_0: The difference in MACE incidence rates between MRI and FFR group is above or equal to δ ??

The outcome will be primarily assessed on an intention to treat basis (mITT) and secondarily on a per protocol (PP) analysis. The null hypothesis H_0 can be rejected and non-inferiority of the MR- guided strategy claimed, if the two-sided 95% confidence interval (CI) for the difference in incidence rates is completely below δ in both the (mITT) and (PP) analysis. A difference of 6%-points was regarded as clinically relevant. Therefore the non-inferiority margin was set to 6%-points.
In addition, absolute and relative frequencies will be given per group. An independent statistician will carry out all statistical analyses. A formal interim analysis is not planned in this study.

For all secondary efficacy variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated for each quantitative variable. Absolute and relative frequencies will be given for categorical data.

3.7.3 COST-UTILITY ANALYSIS

The economic analysis will compare the total costs and effectiveness within each arm of the treatment and provide incremental cost effectiveness ratio (ICER). It will be computed as incremental costs divided by increment quality adjusted life years (QALY). The total costs will include both the direct and indirect costs. Costs will be computed by recording patient utilisation of all NHS services for the follow-up period of one year. These include, for instance, the costs of the initial diagnostic procedures (MRI, coronary angiography and FFR), revascularisation (PCI or CABG), hospitalisation costs, pharmacy costs, optimal medical

therapy costs over the two years plus costs associated with any re-hospitalisation due cardiac events (MI, Repeat Revascularisation). These costs will be assessed using the NHS reference costs. Additional costs will be computed using patient diaries and will include direct health care expenditures plus total time off work (to compute lost income), travel time and any travel or work time costs incurred by home care givers (e.g. spouse, parent, etc.). Quality of Life assessment will be carried out using the EQ5D questionnaire and will be administered at base line and every two months for up to 24 months. Bootstrap methods will be used to derive confidence intervals around the ICER and to derive the Cost Effectiveness Acceptability Curve (CEAC).

3.8 SUMMARY

MR–INFORM is an international, prospective, randomised controlled, non-inferiority outcome trial comparing the role of CMR perfusion to routine coronary angiography with invasive fractional flow measurements for guiding patients with stable angina and an intermediate to high likelihood of coronary artery disease. Non-inferiority of CMR perfusion imaging to the current invasive reference standard (FFR) would establish CMR perfusion imaging as an attractive, non-invasive, alternative to current diagnostic pathways. The results will help to inform national and international guidelines on the investigation and management of coronary artery disease, and ultimately lead to improved patient care.

3.9 STUDY LIMITATIONS

In this prospective outcome trial an important clinical question is addressed. There is currently insufficient evidence on the comparative effectiveness of different diagnostic strategies in patients with stable coronary artery disease and therefore the results of this trial will help to inform future guidelines.

In order to achieve this objective, the trial has been designed to reflect “real-world “ medical practice as closely as possible. This is important for the translation of its results into routine clinical practice. However, inevitably this leads to some limitations in the study design.

Although the aim is to optimise medical therapy in both groups, there are variations on what is deemed optimal in different health systems and the implementation of this is left to the primary care physician. The UK guidelines are followed to minimise variation as much as possible, the remaining variation reflects clinical practice.

A critical point is the inclusion of peri-procedural myocardial infarction and target lesion revascularisation in the end-point. These endpoints are frequently used in interventional trials. The occurrence of peri-procedural myocardial infarction is an important end-point as it is associated with adverse outcome and may reflect better guidance by one technique or the other. However, as revascularisation is guided by objective proof of ischaemia in both arms, it is expected that all patients in the trial are guided towards fewer revascularisation procedures compared to angiography alone and that this will be reflected in low event rates in both arms. The rationale for using target lesion revascularisation is similar.

It is difficult to predict the frequency of crossover from one arm to another that can be substantial (e.g. COURAGE trial). Although a high rate of crossover is not anticipated, the data monitoring committee will assess the occurrence of crossover and allow for adaptation of the randomisation scheme to account for this.

3.9.1 TRIAL STATUS

MR-INFORM is currently recruiting in the UK, Germany, Portugal and Australia. There are currently 9 sites active in the UK, one in Portugal, 5 in Germany and one in Australia. The number of patients recruited at the time of submission is 633.

CHAPTER 4: CORRELATION OF FFR WITH ISCHAEMIC BURDEN MEASURED BY CMR

4.1 INTRODUCTION

In patients with stable coronary artery disease, international guidelines recommend assessment of ischaemia before revascularisation (2). This is based on an accumulating body of evidence showing improved outcome by guiding decisions on revascularisation based on the presence of ischaemia (29, 30, 66, 126). This can be done non-invasively with myocardial perfusion imaging or invasively in the catheterisation laboratory with the measurement of FFR.

FFR is calculated as the ratio between aortic and distal coronary flow at hyperaemia and allows differentiation between flow limiting and non-flow limiting lesions. CMR perfusion imaging allows non-invasive assessment of ischaemia by visualising the first pass of a contrast agent bolus through the myocardium. It enables direct visualisation of a perfusion defect and therefore allows calculation of ischaemic burden as a percentage of the myocardium.

In clinical practice a FFR cut-off value of 0.8 is used for guiding patient management. For perfusion studies most centres use a cut-off value of 10-12.5% ischaemic myocardium for SPECT and 2-3 (out of 32) myocardial segments for CMR.

Several studies have compared the diagnostic accuracy of CMR perfusion imaging and FFR (31, 60, 63). However, a direct comparison between the FFR value and the ischaemic burden measured by CMR has not previously been done.

Therefore, in this study, we sought to determine the relationship between FFR and ischaemic burden measured by high resolution CMR imaging.

4.2 METHODS

A total of 49 patients with typical symptoms (CCS class 1, 2 or 3) of angina were recruited into the study. They underwent CMR perfusion imaging and then angiography with FFR measurement within one month. The local research ethics committee approved the study and all patients gave written informed consent to participate.

Exclusion criteria were any contra-indications to CMR scanning (i.e. claustrophobia, metallic implant, pacemaker insertion), contra-indications to adenosine therapy, previous coronary artery bypass grafts (CABG), recent myocardial infarction (MI) (within 6 months) and left ventricular (LV) ejection fraction <30%.

4.2.1 CMR ACQUISITION

Data were acquired with a 1.5T scanner (Intera, Philips, Best, The Netherlands) using 32-channel coils. Examinations included high-resolution perfusion, cine and scar imaging. Perfusion imaging consisted of 3 short axis slices acquired every heartbeat covering 16 of the standard myocardial segments (apex excluded)(11) first during adenosine stress (140μg/kg/minute of adenosine administered intravenously for 4 minutes) followed by a short axis cine imaging stack and then rest imaging. Imaging parameters for perfusion imaging: k-t blast acceleration factor 5, SSFP sequence, shortest TE (range 1.35-1.54ms), shortest TR (range 2.64-3.12ms), 50° flip angle; 90° prepulse, 100ms prepulse delay and typical acquired resolution 1.7 x 1.9 x 10mm. A dual bolus(127) (equal volumes of 0.0075mmol/kg followed by 0.075mmol/kg after a 20 second pause) of weight adjusted contrast agent (Gadobutrol/Gadovist, Bayer Healthcare, Germany) was injected at 4ml/s by a power injector for stress and rest imaging. The cine images were completed with a set of long axis views. Late Gadolinium enhancement (LGE) images were acquired after 10 minutes (Gadovist 0.2mmol/kg cumulative dose) using an inversion recovery sequence.

4.2.2 CMR IMAGE ANALYSIS

Two independent observers blinded to the angiographic data and clinical history analysed the CMR perfusion images.

A perfusion defect was defined as reduced contrast uptake at stress persisting for ≥4 consecutive dynamic time points but not present at rest. Each observer independently delineated LV endocardial and epicardial borders in all three slices to determine total myocardial area (Osirix software version 5.5.1 64 bit). The ischaemic area was delineated manually with the area of hypoperfusion defined as the area with the least signal intensity

(hypoenhancement) in the stress perfusion dynamic with the clearest delineation of a perfusion defect. In patients with single vessel disease and one perfusion defect, the ischaemic percentage was defined for that vessel as the area of hypoenhancement normalised to ventricular area in all three slice as calculated above. In multivessel disease, with two distinct perfusion defects it was possible to apply the same principle. In a confluent area, if it was difficult to distinguish two separate territories, then an arbitrary 50% division was applied to each. Designation of vascular territories was done according to American Heart Association (AHA) 16-segment classification(128).

In the presence of scar identified as areas of hyperenhancement on late gadolinium imaging, the area of scar was quantified manually and subtracted from the area of hypoenhancement. Inter- observer variability was determined by the comparison of the results from the two observers. Repeating the analysis of 10 cases after an interval of two weeks assessed intra-observer variability.

4.2.3 CORONARY ANGIOGRAPHY AND FFR MEASUREMENT

Standard angiographic views using a Judkin's technique were obtained and patients were anticoagulated with weight-adjusted dose of unfractionated heparin.

Pressure measurements were obtained in all coronary arteries with a diameter >2.5mm and >40% stenosis by visual assessment using a 0.014-inch intracoronary pressure wire (Volcano Therapeutics, San Diego, CA, USA, or Pressure-Wire Certus, St Jude Medical Systems AB, Uppsala, Sweden), during hyperaemia (intravenous adenosine infused at 140μg kg/min). FFR was calculated as P_d/P_a, where P_d and P_a are distal coronary and aortic pressure respectively. A FFR of ≤0.75 was considered significant. Coronary occlusions or lesions of ≥99% were categorised as FFR-positive and a default FFR value of 0.5 was assigned. In cases of serial stenoses, the pressure sensor was positioned beyond the most distal lesion and if the FFR was positive, this was ascribed to the most proximal lesion

4.2.4 ANGIOGRAPHIC ANALYSIS

Angiographic data was analysed offline at the end of the study. Coronary dominance was designated on the basis of the origin of the posterior descending artery. Quantitative assessment of coronary artery percent narrowing was performed with MDQM-QCA (Medcon Limited, Tel Aviv, Israel) software. Entirely smooth and occluded arteries were allocated 0% and 100% respectively.

4.2.5 STATISTICAL ANALYSIS

Data analysis was performed with SPSS version 20 (SPSS Inc., Chicago Illinois). Continuous variables are presented as mean ±SD.

Correlations between normally and non-normally distributed variables were tested by Pearson's and Spearman's methods respectively. Separate analyses were done, including and excluding the CTO data.

Normality of distribution was tested by the Shapiro-Wilk test.

Differences in means between multiple groups were compared using the ANOVA test for normally distributed populations and the Kruskal-Wallis test for non-normally distributed populations.

Inter-observer agreement of perfusion analysis was calculated using the kappa coefficient.

Intra-observer variability was assessed by the use of the coefficient of variation from duplicate measurements

4.3. RESULTS

4.3.1 ANGIOGRAPHIC AND CLINICAL CHARACTERISTICS OF STUDY POPULATION

The study protocol was successfully completed in all patients. Four scans had to be excluded from the CMR analysis due to uninterpretable CMR images, either due to the presence of artefact or the basal slice being too high to allow for accurate assessment of ischaemic

burden. The further analysis relates to the remaining patients. The demographic and clinical characteristics of these patients are listed in table 4.1.

Table 4.1: Pt demographics and clinical characteristics

Parameter		**Number or mean ± SD**
Age (years)		**61.9 ± 9.5**
Sex (male) (n)		**37**
Height (m)		**1.71 ± 0.10**
Weight (kg)		**80.9±14.7**
Body Mass Index		**27.8± 3.8**
CAD risk factors (%)		
	Diabetes	**15.7%**
	Hypertension	**58.8%**
	Smoking	**56.2%**
	Hypercholesterolaemia	**91.3%**
Previous PCI		**12.0%**
Previous myocardial infarction		**7.8%**
Symptoms (%)		
CCS 1		**5.9%**
CCS 2		**85.3%**
CCS 3		**8.8%**
CCS 4		**0**

Drug therapy (%)	
Aspirin	**82.0%**
Statin	**71.4%**
B blocker	**60.0%**
ACE I	**30.0%**

Of all 147 arteries, 59 arteries had a stenosis >40% and were assessed with FFR. 8 vessels were occluded. For angiographic details see table 4.2 and details of the CMR stress perfusion imaging are given in table 4.3.

Table 4.2: Angiographic Characteristics

Parameter	**Number or mean±SD**
No of patients	49
No of FFR measurements (incl CTO's)	59
No of CTO's	8
Vessels with FFR >0.75	21
Vessels with FFR <0.75	38
LAD	21
CX	4
RCA	13
Patients with FFR positive	
1- VD	23

2- VD	7
3-VD	2
QCA in vessels with FFR >0.75 (% diameter stenosis)	49.8± 33.1
QCA in vessels with FFR <0.75 (% diameter stenosis)	85.0± 24.6

Abbreviations: SD – standard deviation: QCA – Quantitative Coronary Angiography

Table 4.3: CMR Perfusion imaging – Haemodynamic parameters

Parameter	**N=49 patients**	
Heart Rate (bpm)	Rest	64
	Stress	80
Systolic Blood Pressure (mmHg)	Rest	136/77
	Stress	134/75
Heart Rate Pressure Product (bpm x mmHg)	Rest	8704
	Stress	10725

4.3.2 COMPARISON OF FFR VALUES AND EXTENT OF ISCHAEMIA

There was very good correlation between the FFR values and the extent of ischaemia in all territories.

Analysis 1 (including occluded vessels): mean values: FFR 0.67±0.17; CMR 8.92±9.35%: r= -0.854, p<0.0005. See fig 4.1.

Analysis 2 (excluding occluded vessels): mean values: FFR 0.69± 0.17; CMR 8.39±9.49: r= -0.849, p<0.005.

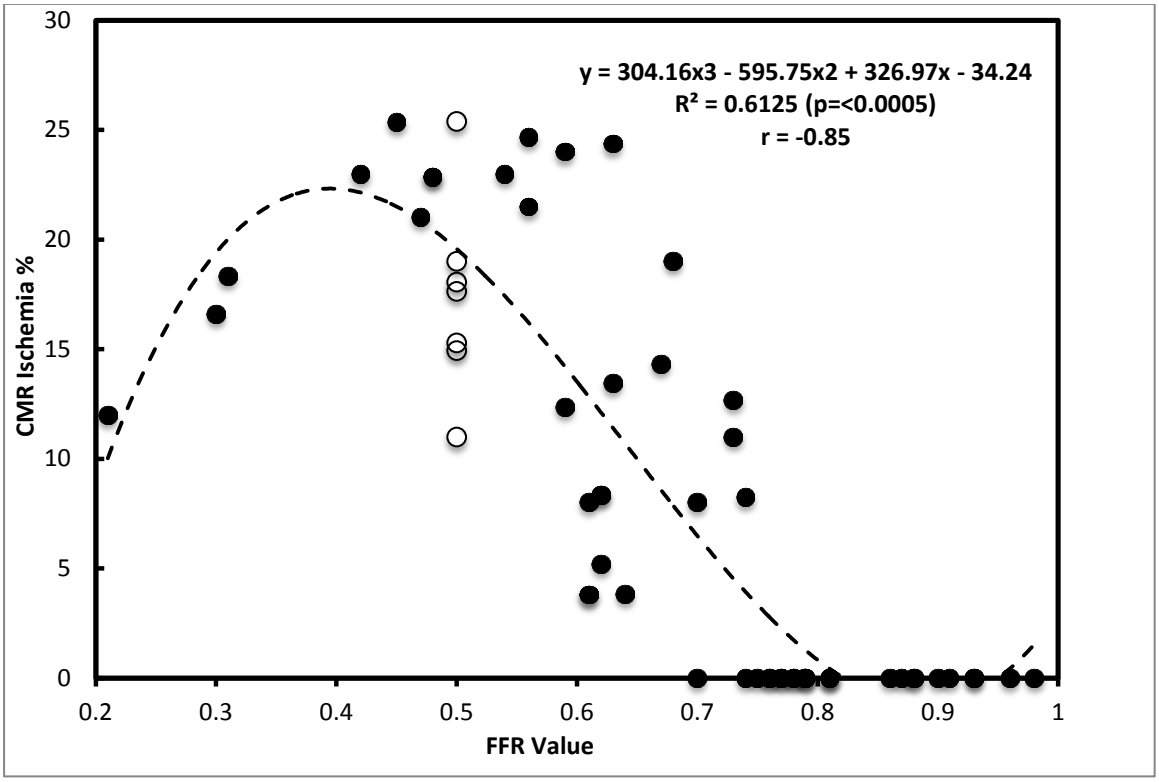


Figure 4.1: Scatter Plot of FFR values and % ischaemia (All values). The FFR values of each vessel have been plotted against the amount of ischaemic myocardium subtended by that vessel. The unfilled dots represent the chronically occluded arteries, which have been assigned a default value of 0.5.

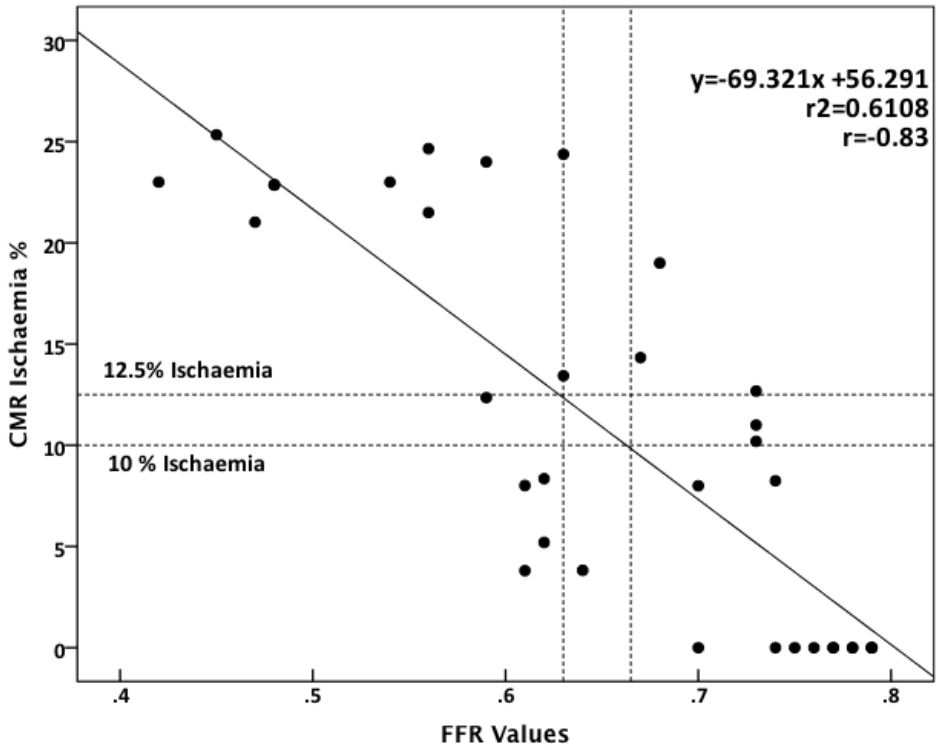


Figure 4.2: Scatter plot between FFR values 0.4-0.8. Scatter plot of FFR values compared to ischaemic burden of the corresponding vessel between the values of 0.4 and 0.8 demonstrating a linear relationship ($p<0.005$). The values for the occluded vessels have been removed and reference lines added to highlight the FFR values of 0.67 and 0.64 that correspond to the prognostically relevant ischaemic burden threshold of 10 to 12.5% respectively.

4.3.3 Analysis of coronary arteries

When considering the different arterial territories individually, the correlation remained good: LAD r= -0.85 ($p<0.005$); CX r= -0.76 ($p=0.80$); RCA r= -0.81 ($p<0.005$). See Figure 4.3

There was no significant difference between the mean values of the three groups: LAD FFR 0.71 ± 0.15, CMR 7.66± 9.0; CX FFR 0.70± 0.21,CMR 9.6± 10.7; RCA FFR 0.61 ± 0.19, CMR 12.2 ±10.2: H =2.178, $p=0.336$. See table 4.4

When considering lesion location within the coronary arteries (analysis done for LAD), mean values are as follows, Proximal LAD: FFR 0.65±0.11, CMR 10.3±8.78; Mid LAD FFR 0.68±0.20,

CMR 8.1±10.4.

4.3.4 Analysis by FFR subgroups

At FFR values greater than 0.75, CMR showed no myocardial ischaemia in any patient. At values between 0.4–0.8 a linear relationship between FFR and CMR with very good correlation was found (r= -0.83, p<0.005). See figure 4.2.

The FFR values that correspond to an ischaemic burden of between 10 – 12.5% are 0.67 and 0.64 respectively and are demonstrated on figure 4.3.

The amount of ischaemia by CMR reached a peak between FFR values of 0.5- 0.4 (mean value 23.0±1.5%). For FFR values <0.4 less ischaemia was found by CMR (mean value 15.6 ±3.2%). There was a statistically significant difference between these three groups: H =35.141, p<0.005. See table 4. 4

Table 4.4: Average CMR and FFR values per coronary territory and per FFR subgroup

Territory		**Mean FFR value**	**Mean CMR value (%)(±SD)**
All arteries		0.67±0.17	8.92±9.35
All arteries (- CTO's)		0.69±0.17	8.39±9.49
LAD	**All values**	0.71 ±0.15	8.01±9.3
	Prox LAD (n=7)	0.65± 0.11	10.3±8.77
	Mid LAD (n=10)	0.68±0.20	8.1±10.4
	LAD in 1VD (n=19)	0.71± 0.13	6.5± 8.7
	LAD in 2-3 VD (n=10)	0.71± 0.13	9.71±10.5
RCA		0.61 ±0.19	12.16±10.3

CX		0.70 ±0.21	9.63±10.8
FFR	**>0.75**	0.81±0.07	0
	0.51-0.75	0.65±0.06	12.7±8.1
	0.4-0.5	0.46±0.02	23.02±1.53
	<0.4	0.27±0.05	15.63±3.2

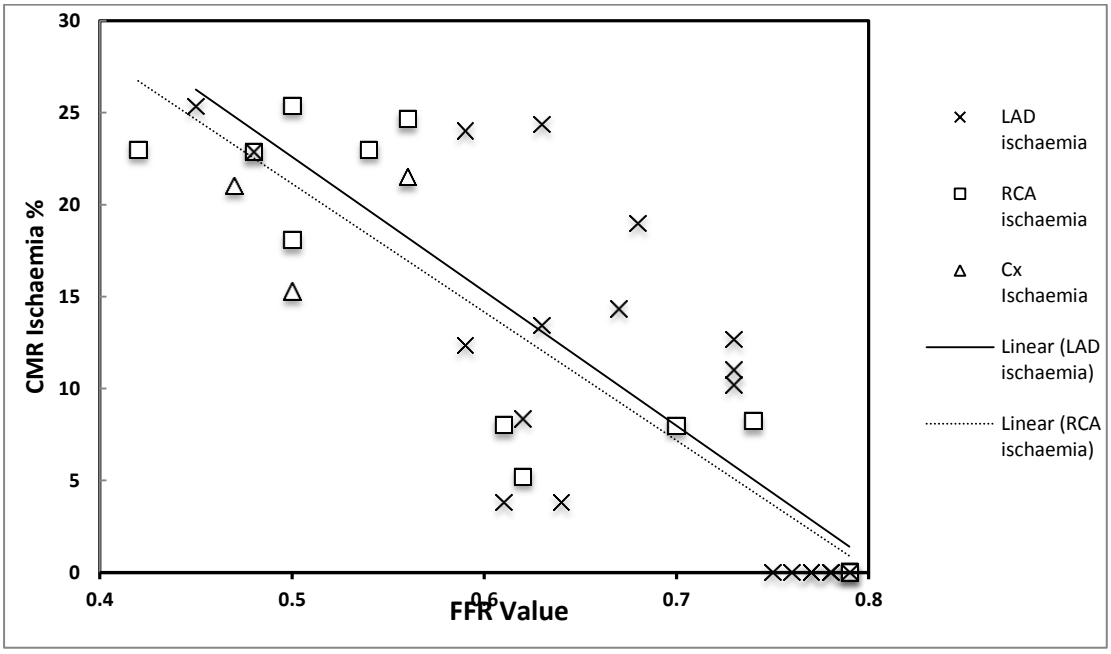


Figure 4.3: Scatter plot demonstrating the relationship between FFR value and percentage ischaemia for the different coronary territories * Too few data points to allow for regression line to be applied to the Cx data

4.3.5 INTER AND INTRA-OBSERVER REPRODUCIBILITY OF ISCHAEMIC BURDEN MEASUREMENT

There was good correlation between the two observers in the measurement of CMR ischaemia with a Kappa coefficient (k=0.826, p=0.048).

Assessment of intra-observer variability demonstrated a co efficient of variation of 13% with a standard deviation of 0.3319.

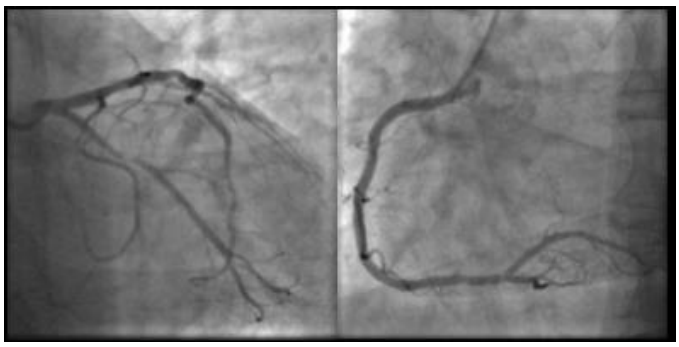


Figure 4.4a

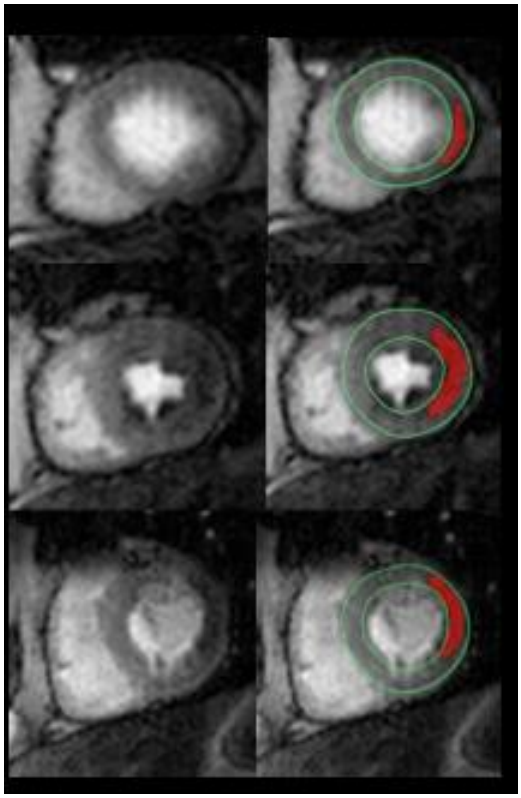


Figure 4.4 b

Figure 4.4: Image of angiographic stenosis (a) and corresponding stress CMR images (b). Figure 4.4a shows the angiographic images with a significant lesion in the circumflex artery.

The FFR value is 0.56. CMR perfusion images (Fig 4.4b) showing the apical, mid and basal slices during stress with a lateral perfusion defect. The endocardial and epicardial borders are delineated (green), the perfusion defect is segmented (red) and calculated as percentage of the total myocardial area. In this case, the amount of ischaemia measured is 21.5%.

4.4 DISCUSSION

This study demonstrates a number of findings:

1) FFR values between 0.75 and 0.4 correlate closely with the ischaemic burden as determined by CMR perfusion imaging.
2) An FFR value of greater than 0.75 is associated with no myocardial ischaemia.
3) The most extensive myocardial ischaemia is found for FFR values between 0.4 and 0.5.
4) The maximum amount of ischaemia caused by one artery is 25% of the myocardium.

4.4.1 FFR AND ISCHAEMIC BURDEN

FFR is an index of the physiological importance of a particular stenosis and its effect on flow within the artery and therefore indicates the presence of ischaemia(129). A significant FFR is currently used as a dichotomous variable signifying presence or absence of myocardial ischaemia. However, the relationship between FFR value and extent of myocardial ischaemia is poorly understood.

In this analysis, it has been demonstrated for the first time, that there is good correlation between the severity of a narrowing and the extent of ischaemia. This is important for a number of reasons: firstly, it further validates the utility of FFR for the functional assessment of coronary lesions. Secondly, it demonstrates that the severity of FFR is related to the extent of myocardial ischaemia. A larger pressure drop across a coronary stenosis is indicative of greater flow limitation resulting in a lower FFR value. Our study confirms that this relationship translates into a larger ischaemic burden. Thirdly, it allows the development of FFR as a tool to assess ischaemic burden.

The maximum extent of ischaemia measured was 25% in patients with FFR values in the range of 0.4- 0.5. This seems to be the maximum myocardial area subtended by a single coronary artery. This observation was the same in all three arteries and is also observed in a recent 3D CMR perfusion study by Manka et al (65).

Lesion location is also an important consideration and our results suggest greater ischaemia with a proximal LAD lesion than a mid LAD lesion despite similar FFR values. The complex inter-relationship between lesion location, FFR value and ischaemic burden is interesting to define, but requires much larger numbers of patients and is a potential subject for subanalysis once the MR-INFORM study is completed.

A recent study by Leone et al also investigated the relationship between FFR and the amount of myocardium perfused (112). They analysed 213 intermediate stenoses (30- 80% visual estimate) in 184 patients and found that lesions located in the proximal LAD were related to significantly lower FFR values and to a higher rate of positive FFR than those in the distal LAD, CX and RCA. However, this study is limited by lack of direct assessment of the amount of ischaemia caused which is calculated indirectly by myocardial jeopardy scores instead.

FFR is also affected by diameter stenosis and minimal lumen area (130). It is noteworthy, that even in the absence of controlling for similar lesion location and arterial diameter, we have demonstrated good correlation, suggesting that the actual FFR value may be one of the more important variables affecting extent of ischaemia.

For FFR values less than 0.4, a decrease in the extent of myocardial ischaemia was observed. This is unexpected and it is difficult to lay too much emphasis on this, as the numbers are small. While we are unable to provide a clear understanding of this phenomenon it is interesting to postulate on the role of collaterals and pre-conditioning.

4.4.2 Clinical Implications

Data from SPECT (69, 126) and CMR increasingly supports the notion that revascularisation should be restricted to those patients with *significant*, rather than the pure *presence* of ischaemia. In the current data, significant ischaemia as defined by an ischaemic burden of 10-12.5% (66) on the CMR perfusion scan only occurred at FFR values of approximately 0.63-

0.67 (See Fig 2). Revascularisation could thus be targeted to these values but this relates to single vessel disease only. In patients with multivessel disease, revascularisation maybe targeted to the vessel with the lowest FFR result resulting in a greater reduction in ischaemic burden.

This strategy is also supported by recent data from the FAME 2 trial (30), which suggests that the benefit in the PCI group may be related to the area of ischaemia associated with the FFR value. They demonstrated that the effects of PCI appeared to be more pronounced among patients who had lesions with an FFR of less than 0.65 than among patients who had only lesions with larger FFR values ($p<0.01$). This is the first time that the importance of the FFR value itself has been related to the endpoints of the trial. The data would suggest that the mean FFR value of 0.68 in the trial corresponds to prognostically significant ischaemic burden and thus would explain the benefit in the PCI group. However, whether this benefit translated into a reduction in hard endpoints remains unanswered due to the premature termination of the trial. Thus, future studies need to focus on further fine-tuning FFR to guide patients with mild ischaemia.

4.4.3 STUDY LIMITATIONS

This study has a number of limitations. The sample size in this study is modest.

The polynomial fit has been used to include the values less than FFR 0.4 but caution has to be used in interpreting these, as the numbers are few. However, this is the first study of this kind and much larger sample sizes will be required to investigate how ischaemic burden varies with lesion location and vessel size as alluded to earlier in the text.

The matching of angiographic coronary arteries with territories on non-invasive imaging can never be exact potentially leading to inaccuracies in assessment and allocation of ischaemic burden. Additionally, assessing the relative contribution of two coronary arteries to one large area of perfusion defect involving adjacent territories is very subjective.

For this study, qualitative visual assessment was used to reflect normal clinical practice. Fully quantitative perfusion analysis measuring absolute myocardial perfusion is slowly becoming available and may allow more accurate assessment of ischaemic burden.

4.5 CONCLUSION

There is good correlation between FFR values and the extent of myocardial ischaemia. FFR values above 0.75 are not associated with myocardial ischaemia and ischaemic burden increases linearly with smaller FFR values until a maximum ischaemia of 25% is found in myocardium subtended by arteries with FFR values between 0.4 and 0.5. This information could potentially be used to target revascularisation to a subgroup of patients with a positive FFR and high ischaemic burden.

CHAPTER 5: VALIDATION OF A FUNCTIONAL JEOPARDY SCORE WITH CMR PERFUSION IMAGING

5.1 INTRODUCTION

Functional information on the significance of a coronary artery stenosis is increasingly used to decide on the management of patients with coronary artery disease (CAD)(1). Using FFR to guide lesion revascularisation by percutaneous intervention (PCI) leads to a reduction of Major Adverse Cardiac Events (MACE)(131, 132). However, FFR only assesses whether the blood flow to a certain myocardial territory is sufficient, but does not provide any information on the myocardial volume subtended by the stenotic coronary artery. This information is important as only patients with >10-12.5% ischaemic myocardium profit from revascularisation(66).

To overcome this limitation of invasive angiography several jeopardy scores have been developed and validated(70, 71). These scores are based on the location and anatomical severity of coronary lesions and do not directly incorporate the functional significance of a stenosis. The recently described functional Syntax score (133) integrates complex anatomical data that determines the classical syntax score with FFR assessment of the relevant vessels, providing a more accurate risk assessment of the angioplasty procedure. However, the Syntax score is complex to use, time consuming, has high inter-observer variability and provides information on risk of the procedure rather than ischaemic burden. Whether this same principle can be applied to classical jeopardy scores, to produce “functional jeopardy scores” that provide a more accurate assessment of the myocardium at risk by the incorporation of FFR data, remains unknown.

The aim of the current study is to combine functional and anatomical information obtained in the catheterisation laboratory to develop a functional jeopardy score and assess the anatomical (classical) as well as the physiological scores against ischaemic burden measured by high-resolution CMR perfusion imaging.

5.2 METHODS

5.2.1 PATIENT POPULATION

The local research ethics committee approved the study and all patients gave written informed consent to participate. 45 patients with stable angina (CCS class 2 or 3) and two risk factors for CAD awaiting invasive angiography underwent CMR scanning followed by coronary angiography (CXA) and FFR measurement within one month.

Exclusion criteria were contra-indications to CMR scanning or adenosine, previous CABG or recent PCI, renal failure with an eGFR<30, known LV ejection fraction <35% and unstable symptoms.

5.2.2 CMR ACQUISITION

Data were acquired with 1.5T scanners (Intera, Philips, Best, The Netherlands) using 32-channel coils. Examinations included high-resolution perfusion, cine and scar imaging. Perfusion imaging consisted of 3 short axis slices acquired every heartbeat covering 16 of the standard myocardial segments (apex excluded)(11) first during adenosine stress (140μg/kg/minute of adenosine administered intravenously for 3 minutes) followed by a short axis cine imaging stack and then rest imaging. Imaging parameters for perfusion imaging: k-t blast acceleration factor 5, SSFP sequence, shortest TE (range 1.35-1.54ms), shortest TR (range 2.64-3.12ms), 50° flip angle, 90° prepulse, 100ms prepulse delay and typical acquired resolution 1.7 x 1.9 x 10mm. A dual bolus(127) (equal volumes of 0.0075mmol/kg followed by 0.075mmol/kg after a 20 second pause) of weight adjusted contrast agent (Gadobutrol/Gadovist, Bayer Healthcare, Germany) was injected at 4ml/s by a power injector for stress and rest imaging. The cine images were completed with a set of long axis views. Late Gadolinium enhancement (LGE) images were acquired after 10 minutes (Gadovist 0.2mmol/kg cumulative dose) using an inversion recovery sequence.

5.2.3 CMR IMAGE ANALYSIS

Two independent observers blinded to the angiographic data and clinical history analysed CMR perfusion images. A perfusion defect was considered present if reduced contrast uptake was seen at stress, persisting for ≥ 4 consecutive dynamic time points, but not present at rest. Each observer independently delineated LV endocardial and epicardial borders to determine myocardial area (Osirix software v 5.5.1. Pixmeo, Switzerland). The ischaemic area was delineated manually with the area of hypoperfusion defined as the area with the least signal intensity (hypoenhancement) in the stress perfusion dynamic with the clearest delineation of a perfusion defect. The total ischaemic area was calculated by summation of the hypoperfused areas. In cases of scar, identified as areas of hyperenhancement on late gadolinium imaging, the perfusion defect including the scarred area was included in the analysis. Inter- observer variability was determined by the comparison of the results from the two observers. Repeating the analysis of 10 cases after an interval of two weeks assessed intra-observer variability.

5.2.4 CORONARY ANGIOGRAPHY

CXA was performed within one month of CMR scanning. Standard angiographic views using a Judkin's technique were obtained.

Intra-coronary pressure measurements were obtained in all coronary arteries with a diameter >2mm and >50 % diameter stenosis by visual assessment using a 0.014-inch intracoronary pressure wire (Volcano Therapeutics, San Diego, CA, USA, or Pressure-Wire Certus, St Jude Medical Systems AB, Uppsala, Sweden). FFR was calculated as P_d/P_a during hyperaemia (intravenous adenosine infused at 140 micrograms kg/min), where P_d and P_a are distal coronary and aortic pressure respectively. A FFR of <0.75 was considered significant. Coronary occlusions or lesions of ≥99% were defined as FFR positive. In cases of serial stenoses, the pressure sensor was positioned beyond the most distal lesion and if the FFR was positive, this was ascribed to the most proximal lesion

5.2.5 ANGIOGRAPHIC ANALYSIS AND JEOPARDY SCORING

An experienced observer blinded to the CMR imaging and clinical data analysed the angiographic images. Quantitative coronary angiography (QCA) was performed with MDQM-QCA (Medcon Limited, Tel Aviv, Israel) software.

Jeopardy scores were calculated according to the Alberta provincial project for Outcome Assessment in Coronary Heart Disease Score (APPROACH) score(72) and the BCIS score (71, 73). The APPROACH anatomical score divides the left ventricle into regions according to pathological studies in humans evaluating the relative proportion of myocardium perfused by each coronary artery. In the modified version, the vessel dominance, site of occlusion and size of the major branches of the infarct related artery are taken into consideration (Table 5.1).

The BCIS score is a contemporary score(71, 73), derived from the Duke score. The Duke Jeopardy score is calculated by dividing the coronary tree into six segments of nearly equal myocardial perfusion (i.e. left anterior descending artery, major septal perforator, major diagonal branch, circumflex artery, major obtuse marginal artery and posterior descending artery). A score of two is given for each significant lesion in a myocardial territory. The BCIS score allows for the classification of graft and left main stem disease by ascribing points to a left main lesion of >50% and to significant graft lesions. The total BCIS score was divided by 12 to provide a percentage of ischaemia as required in the Bland Altman analysis etc.

The jeopardy scores were calculated based on the QCA results using two accepted thresholds of luminal diameter reduction to define lesion significance: 70% (APP_{70} and $BCIS_{70}$) and 50% stenosis (APP_{50}, and $BCIS_{50}$).

Table 5.1: Modified Angiographic APPROACH score. Results provided as a percentage of the left ventricular myocardium. Modified from Ortiz-Perez et al (134)

Culprit lesion	**Infarct related artery side branches**		**Diagonal for LAD occlusion only or posterolateral for all others**		
			Small/Absent	Medium	Large
LAD (RD		Distal	13.75	14.8	15.9

or LAD)		Mid	27.5	29.7	31.8
		Proximal	41.25	44.5	47.75
Proximal LCx (RD)	OM	Small/Absent	9.25	12.5	15.75
		Medium	15.25	18.5	21.75
		Large	21.25	24.5	27.75
Proximal LCx (LD)	PDA	Small/Absent	23.5	28	32.5
		Medium	29.5	34	38.5
		Large	35.5	40	44.5
MID LCx (LD) or RCA (RD)	PDA	Small/Absent	9.25	12.5	15.75
		Medium	15.25	18.5	21.75
		Large	21.25	24.5	27.75
Mid LCx (RD)			3.25	6.5	9.75

Abbreviations: APPROACH score =Alberta provincial project for Outcome Assessment in Coronary Heart Disease Score: LAD = left anterior descending artery, LCX =left circumflex artery, LD=left dominant, RD=right dominant, RCA=right coronary artery, OM=obtuse marginal artery, PDA=posterior descending artery.

5.2.6 FUNCTIONAL JEOPARDY SCORE

The functional scores using the APPROACH (f-APP) and the BCIS (f-BCIS) jeopardy scores were calculated based on the FFR results alone. Additionally, a weighted functional- APPROACH score was calculated as the product of the APPROACH score and (1-FFR value). This allowed for a greater ischaemic burden to be calculated for lower FFR values and vice versa.

5.2.7 STATISTICAL ANALYSIS

Statistical Analysis was performed using IBM SPSS Statistics (version 19 SPSS, Chicago, Illinois and Medcalc (v12.3.0, Mariakerke, Belgium). Continuous variables were expressed as mean +/- SD. Correlations between normally and non-normally distributed variables were tested by Pearson's and Spearman's methods respectively. The correlation between the functional and anatomical jeopardy scores and the extent of ischaemia measured by CMR was assessed. Agreement between the two tests was tested with the Bland-Altman analysis. Normality of distribution was tested by the Shapiro-Wilk test. The Fisher to z transformation was used to assess the significance of the change in correlations. Inter-observer variability of perfusion analysis was calculated using the kappa coefficient.

Receiver-operating characteristic (ROC) analysis determined the accuracy of the f-APP and the f-BCIS scores to predict 12% ischaemia on CMR. Intra-observer variability was assessed by the use of the coefficient of variation from duplicate measurements. For all analyses $P<0.05$ was considered significant.

5.3 RESULTS

5.3.1 CLINICAL CHARACTERISTICS

45 patients (mean +/- SD age, 62+/-10 yrs) were included in the analysis. For the demographic and clinical characteristics see table 5.2.

Table 5.2: Patient demographics and clinical characteristics

Parameter	**Number (%) or mean (SD) (n=45)**
Age (years)	**61.9 (9.5)**
Sex (male) (n)	**27**
Height (m)	**1.72 (0.10)**
Weight (kg)	**82.7 (14.71)**

Body Mass Index		**27.8 (3.8)**
CAD risk factors (%)		
	Diabetes	**11.4**
	Hypertension	**51.4**
	Smoking	**69.0**
	Hypercholesterolemia	**86.7**
Previous PCI		**11.7**
History of Previous myocardial infarction		**11.4**
Angina Symptoms (%)		
CCS 1		**5.9**
CCS 2		**85.3**
CCS 3		**8.8**
CCS 4		**0**
Drug therapy (%)		
Aspirin		**91.1**
Statin		**82.6**
B blocker		**61.7**
ACE I		**29.4**

Abbreviations: PCI-percutaneous intervention: CCS- Canadian Class score: ACE – Angiotensin-converting enzyme inhibitor

5.3.2 ANGIOGRAPHIC AND FFR RESULTS

Three patients had visually unobstructed arteries where no FFR measurement was done. On the basis of QCA measurements, 59 arteries had stenoses >50 % and 37 arteries had stenoses >70%.

FFR was measured in 58 arteries (a pressure measurement was not performed in one artery due to technical reasons and 10 arteries were CTO's or subtotal occlusions). Of these, 26 arteries had an FFR above 0.75 and 32 had a FFR <0.75 (table 5.3).

Based on FFR measurements alone, 15 patients had no functional coronary disease, 15 patients had single vessel disease, 4 patients had 2-vessel disease and 2 patients had 3-vessel disease.

Table 5.3: Angiographic details

Parameter		**Number**
No of patients		36
No of FFR classifications (incl CTO's)		58
Vessels with FFR >0.75		26
Vessels with FFR <0.75		32
	LAD	15
	LCx	6
	RCA	6
	D1	2

	OM1	2
	OM2	1
One vessel disease		16
Two vessel disease		4
Three vessel disease		2

5.3.3 CMR FINDINGS

Three patients were excluded from the CMR data analysis due to poor image quality. Three patients had scar on LGE. The mean ischaemic burden measured on CMR was 11.21 +/-11% **(**table 5.4).

Table 5.4: CMR data

	Number or mean (SD)
No of patients	36
Rest HR	63.7 (12.0)
Rest SBP	134 (21.3)
Rest RPP	7089
Stress HR	75.5 (21.3)
Stress SBP	127 (24)
Stress RPP	8353
Ischaemia burden (%)	11.2 (11)

Table 5.4: CMR data. Abbreviations**:** HR=heart rate: SBP= systolic blood pressure: RPP= rate pressure product

5.3.4 Correlation and agreement between CMR and angiographic assessment of extent of ischaemia

The mean score for APP_{50} was 40.36 +/- 26% and 33.81% +/-25% for APP_{70}. The mean f -APP score was 23.97 +/- 23.4 (table 4)

The mean score for $BCIS_{50}$ was 4.4 +/- 3.1 and 3.73 +/- 3.17 for $BCIS_{70}$. The f-BCIS score was 2.78 +/-2.7 (table 5.5).

The correlation between percentage ischaemia measured by CMR and the APP_{50} score (r=0.58 p=0.0001) was moderate. The correlation with the APP_{70} was r=0.66 (p=0.0001) with and r=0.82 (p=0.0001) with the f-APP (figure 5.1). The change in correlation between APP_{50} and f-APP was significant z statistic=-2.04,p=0.04 whereas APP70 and f-APP did not differ significantly (z= -1.51, p=0.131).

Bland Altman analysis reveals that in relation to CMR, the APP_{50} and APP_{70} overestimated the volume of ischaemic myocardium by 29.2% and 22.6% respectively, which was reduced to 12.8 % after integrating functional data (table 5.5). An f-APP score of 26% corresponded to a CMR ischaemia threshold of 12% (Fig 5.1c).

The correlation between the $BCIS_{50}$ score and CMR was r=0.48, p=0.0001 and r=0.63 p=0.0001 with $BCIS_{70}$ (fig 5.2). For the f-BCIS score r=0.82, p=0.0001. The change in correlation between $BCIS_{50}$ and f-BCIS was significant (z statistic -2.63, p= 0.009), however, $BCIS_{70}$ and f-BCIS did not differ (z statistic -1.51, p=0.13).

An overestimation of ischaemic burden was demonstrated with the BCIS scores (mean bias: $BCIS_{50}$: 25.2%, $BCIS_{70}$: 19.9%, f-BCIS: 12%)(table 4). A f-BCIS score of 3 corresponded to a CMR ischaemia threshold of 12% (Fig 5.2c).

Using the weighted APPROACH (APP X (1-FFR value)) score resulted in better agreement with a mean bias of 1.1% (Fig 4).

Table 5.5: Mean values of angiographic scores and correlation with CMR

Score		**Mean result (+/- SD)**	**Correlation with CMR (r value)**	**Significance**	**Mean bias %**
APPROACH	**APP_{50}**	40.37 (26)	0.58	p<0.05	29.9
	APP_{70}	33.82 (27.8)	0.66	p<0.05	22.6
	f-APP	23.97 (23.4)	0.82	p<0.05	12.8
BCIS	**$BCIS_{50}$**	4.37 (3.1)	0.48	p<0.05	25.2
	$BCIS_{70}$	3.74 (3.17)	0.63	p<0.05	19.9
	f-BCIS	2.79 (2.7)	0.82	p<0.05	12.0

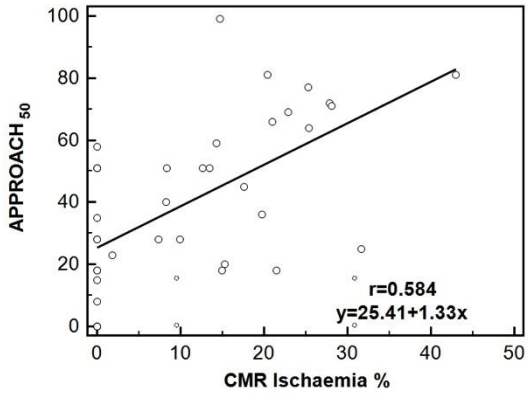


Fig 5.1a

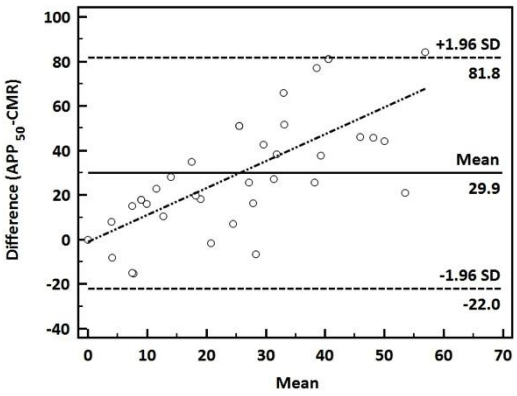


Fig 5.1d

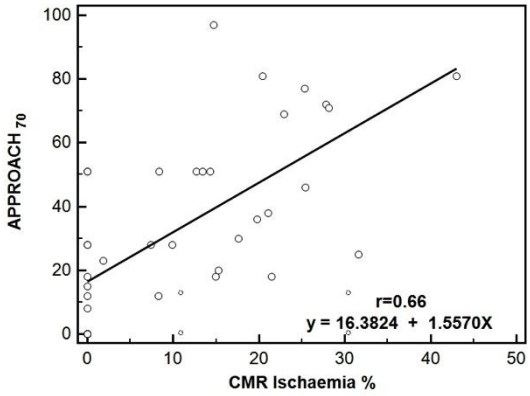


Fig 5.1b

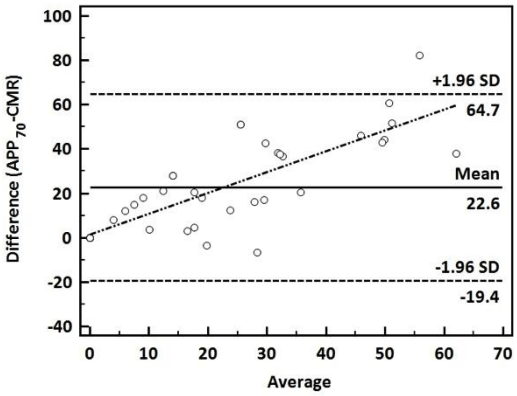


Fig 5.1e

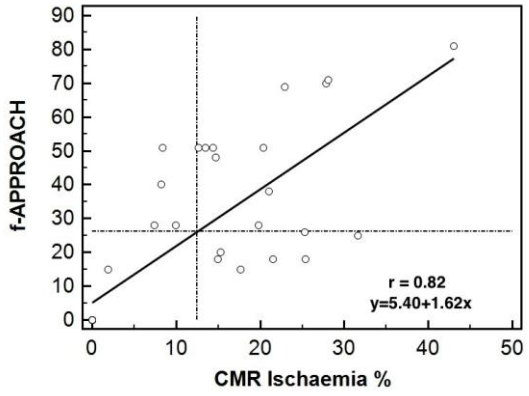


Fig 5.1c

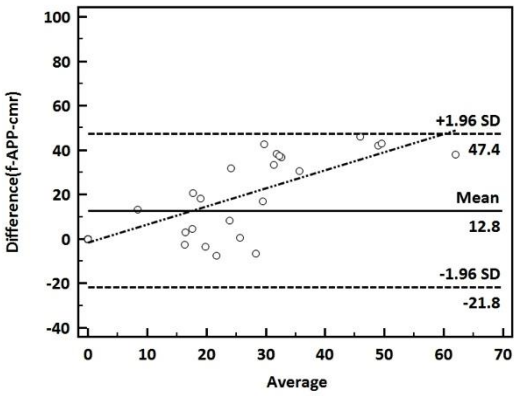


Fig 5.1f

Figure 5.1: Correlation and Agreement between CMR and the APPROACH jeopardy score.

Scatter plots illustrating the correlation between the extent of ischaemia measured by CMR compared to that assessed by the APPROACH jeopardy score based on thresholds of 50% (5.1a) and 70% (5.1b) for significance and on FFR (5.1c). Corresponding Bland Altman plots (5.1d-5.1f) with limits of agreement lines (2SDs). The prognostically important threshold of 12% ischaemic burden is highlighted by the dashed vertical line (5.1c) and corresponds to a f-APPROACH score of 26%.

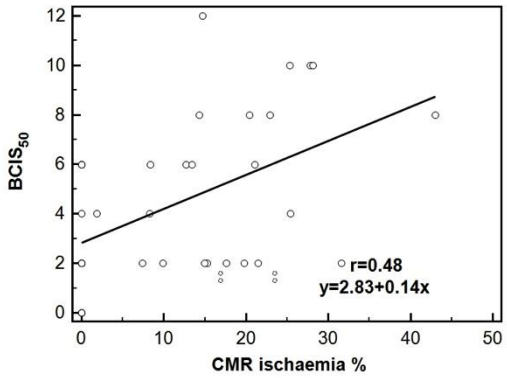


Fig 5.2a

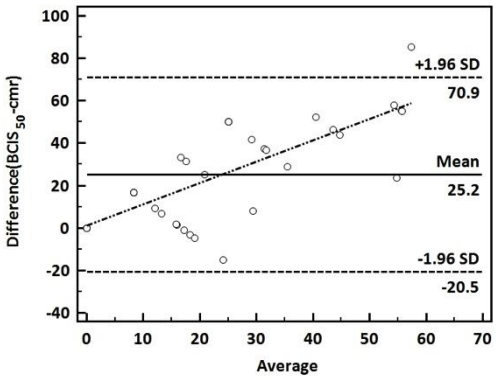


Fig 5.2d

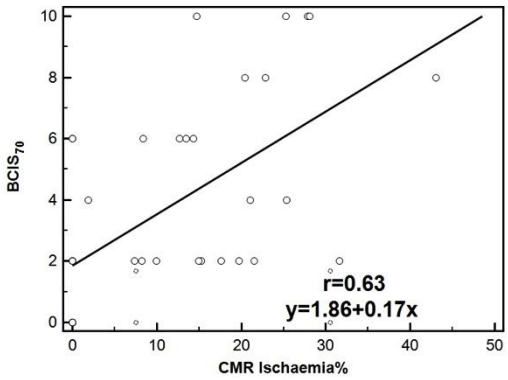


Fig 5.2b

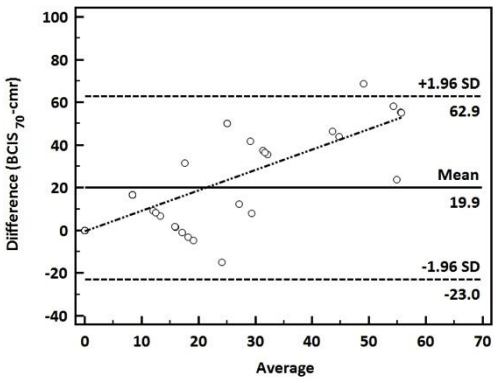


Fig 5.2c

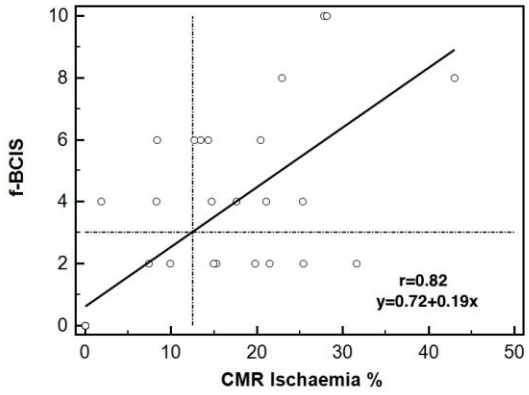


Fig 5.2c

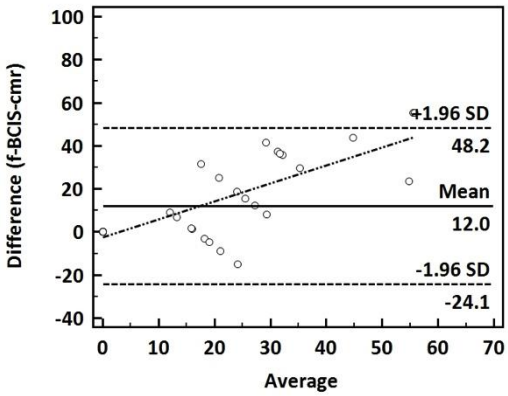


Fig 5.2f

Figures 5.2: Correlation and Agreement between CMR and the BCIS jeopardy score.

Scatter plots illustrating the correlation between the extent of ischaemia measured by CMR compared to that assessed by the BCIS jeopardy score based on thresholds of 50% (5.2a) and 70% (5.2b) for significance and on FFR (3c). Corresponding Bland Altman plots (5.2d-5.2f) with limits of agreement lines (2SDs). The prognostically important threshold of 12% ischaemic burden is highlighted by the dashed vertical line (5.2c) and corresponds to a f-BCIS score of 3.

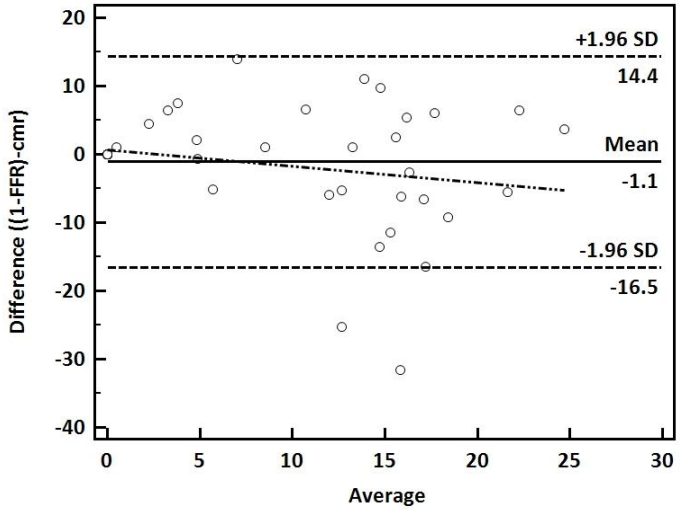
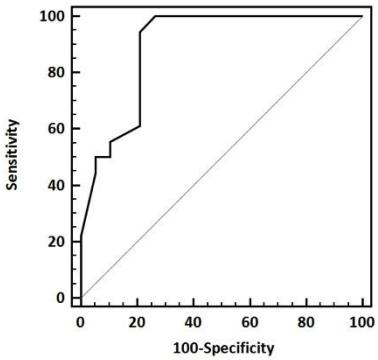


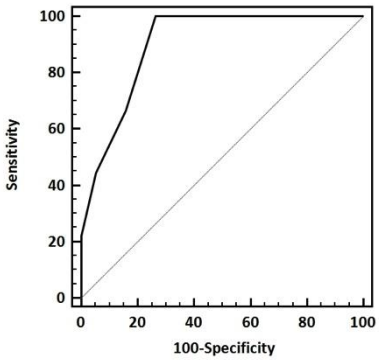
Figure 5.3: Weighted APPROACH score

Bland Altman analysis demonstrating the agreement between the weighted APPROACH score and the extent of ischaemia demonstrated by CMR. The weighted APPROACH score is calculated as the product of 1- FFR value and the APPROACH score and demonstrates improved agreement with a mean bias of -1.1%

5.3.5 DIAGNOSTIC ACCURACY OF THE FUNCTIONAL JEOPARDY SCORES TO DETECT ISCHAEMIA >12%

The area under the ROC curve (AUC) for the f-APP and the f-BCIS scores to accurately predict ischaemia >12% is 0.893 (95%CI: 0.748-0.940) and 0.901 (95% CI: 0.757-0.974) respectively. An f-APP score of 26% results in a sensitivity of 62% and a specificity of 79% to detect a threshold of 12%. A f-BCIS score of 3 has a sensitivity of 55% and a specificity of 90% to detect this threshold (Fig 5.4).





5.4a 5.4b

Figure 5.4: Receiver Operating Characteristic curve for f-APP and f-BCIS and Jeopardy Score to detect myocardial ischaemic burden ≥12%.

A f-APP score (5.4a) of 3 detected this threshold with sensitivity 62% and specificity 79%. A f-BCIS score (5.4b) of 26% detected this threshold with a sensitivity of 55% and a specificity of 90%.

5.3.6 REPRODUCIBILITY

Inter-observer variability in the measurement of CMR ischaemia was good (k=0.826, p=0.048). Intra-observer variability demonstrated a co-efficient of variation of 13% with a SD of 0.3319.

5.4 DISCUSSION

Functional jeopardy scores correlate well with the ischaemic burden as determined by CMR perfusion imaging. There is significant overestimation of the ischaemic burden by anatomical jeopardy scores, which is reduced by adding the functional information.

Since CXA is often performed without prior testing for ischaemic extent and severity, there is a need to assess the significance of ischaemia in the catheterisation laboratory. However, due to the disparity of functional and anatomical information (135) the accurate estimation of ischaemic extent by classical anatomical jeopardy scores is questionable. While functional measurements of stenosis significance by FFR are more predictive of outcome than the anatomical severity, FFR does not take the extent of the defect into account. For example, a positive FFR in an artery supplying a small territory may result in very little demonstrable ischaemia at a myocardial level.

The novel functional jeopardy score proposed in this manuscript incorporates information on stenosis severity and the amount of myocardium subtended by the artery. This approach improves the estimate of ischaemic extent when compared to CMR as the reference standard (Fig 5.5).

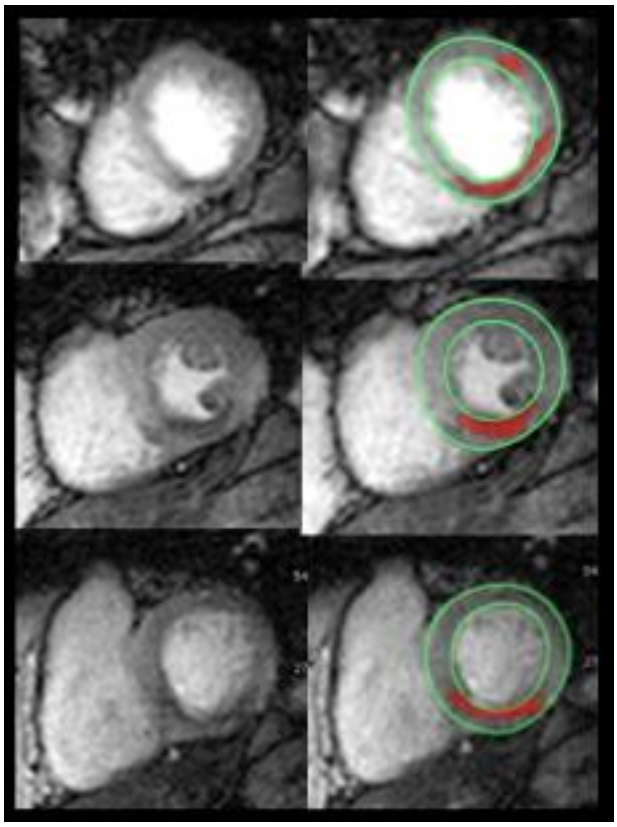


Fig 5.5a

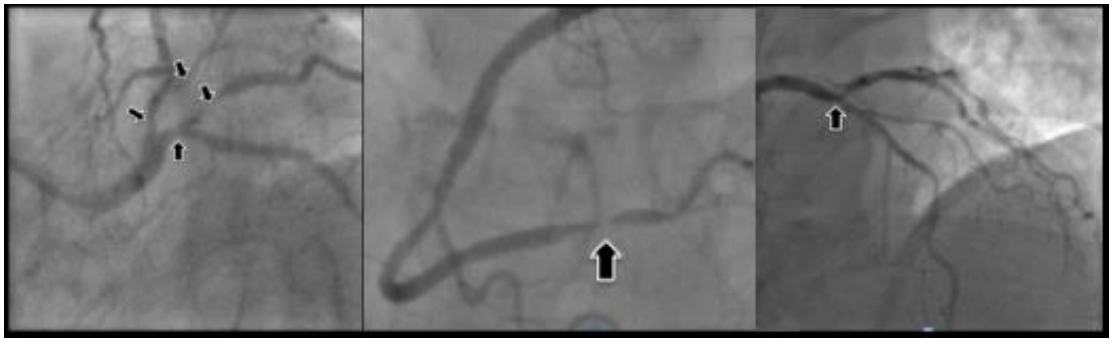


Fig 5.5b

Figure 5.5: Case Example

Perfusion images of the apical, midventricular and basal slices with delineation of the endocardial and epicardial borders and measurement of ischaemic burden (Fig 5.5a). Hypoenhancement in the inferior wall is seen in all three slices, which would be consistent with ischaemia of the RCA. Additionally a small area is seen in the apical anterolateral wall that would be consistent with ischaemia in either the marginal or diagonal branches in which the FFR result is also positive. The amount of ischaemic myocardium is measured at 19%.

Corresponding angiographic images (Fig 5.5b) demonstrating the significant lesions within the RCA as well as the LAD, and LCx arteries. Lesions within the OM and diagonal branches are also seen. Fig 5.5c shows the FFR result in the vessels interrogated. Based on the angiographic images, the APP score for area at risk is 89% and the BCIS score is 10 (Fig 5.5d). However, as the LAD and Cx arteries are FFR negative the score is reduced to 51% and to 4.

Artery	**QCA (%)**	**FFR**
LAD	72	0.79
Diagonal	70	0.69
Cx	67	0.93
OM1	82	0.61
RCA	80	0.30

Fig 5.5c

Ischaemic burden	**Score**
CMR ischaemia	19%
APP score	89%
BCIS score	10
f-APP score	51%
f- BCIS score	4

Fig 5.5d

Previous comparative studies between CMR and FFR have assessed the diagnostic accuracy of CMR using FFR as the reference standard(63, 136) but CMR is now increasingly utilised to assess ischaemic burden. In a recent study, Jogiya et al measured ischaemic burden by visual

analysis of CMR images(32) demonstrating good correlation with the Duke Jeopardy score (r=0.82). Morton et al showed that a BCIS score ≥6 predicts an ischaemia threshold of 12% on CMR with high specificity(137). However, both of these studies have used an anatomical score, without correction for haemodynamic relevance.

While confirming a good correlation, marked disagreement in the estimation of ischaemic volume is noted. This may be a consequence of underestimation by CMR, overestimation by the jeopardy scores, or a combination of both and could potentially be explained by limitations of jeopardy scoring.

The APPROACH score is based on pathological post-mortem studies of hearts with occluded arteries(138, 139) and includes areas of infarction, risk zones and no reflow zones and thus will be significantly larger than areas of ischaemia in non-occluded arteries. This suggests that an overestimation by the angiographic scores may be responsible for the discordance.

The extent of the area at risk has been compared previously in patients presenting with acute myocardial infarction. The Duke and the APPROACH score were both used by Berry et al who compared the extent of the area at risk with CMR T2 weighted imaging and angiographic scoring(140) demonstrating reasonable correlation ($r=0.66$, $p<0.0001$). Similarly, Fuernau et al also used the APPROACH score to compare the angiographic area at risk with the CMR area at risk ($r=0.87$, $p<0.001$) (141). Both studies showed an overestimation of T2 weighted area at risk in relation to angiographic area at risk by the APPROACH score due to inclusion of both the infarcted area and surrounding oedema.

In patients with stable CAD, ischaemia may be the consequence of diffuse disease, for which the precise lesion responsible for ischaemia is harder to pinpoint, resulting in discrepant estimation. Furthermore, collaterals that develop during chronic ischaemia will reduce the ischaemic area. A recent study by Arnold et al (142) used the Bypass Angioplasty Revascularisation Investigation (BARI) myocardial jeopardy index and the DUKE score to assess angiographic disease burden in patients with multi-vessel CAD. Using fully quantitative analysis, hyperaemic blood flow was evaluated and ischaemic burden was quantified. They also found that relative to cardiovascular magnetic resonance, angiographic assessment overestimated disease burden at baseline (CMR 49.9±29.2% versus BARI 80.7±15.2%

[P<0.0001] and Duke 64.5±29.6% [P=0.0019]). This again may be a reflection of the limitation of using a jeopardy score and also of pure anatomical assessment.

The BCIS score is derived from the Duke jeopardy score, which was developed based on the usual distribution of coronary arteries to more accurately define CAD than a simple classification into 1-, 2- or 3 vessel disease. As it is purely a weighted score its utility in estimating actual percentage ischaemic burden may be limited. Interestingly, however, when converted to a percentage, the amount of myocardium at risk is very similar to that measured by the APPROACH score (Figure 2) and the correlation and extent of ischaemia measured by the functional scores are almost identical (f-APPROACH r=0.82, isch = 23%; f-BCIS r=0.82, isch= 22%).

Using a weighted APPROACH score that takes into account the FFR value assuming that the lower the FFR value the greater the ischaemic extent, results in almost perfect agreement. This suggests that value of FFR (when considered as a continuous variable) provides information on the severity of ischaemia, over and above the dichotomous classification that is currently used. Recent subanalysis data from the FAME 2 trial(30) also hints at this by demonstrating that in proximal lesions within large arteries, patients with an FFR value of less than 0.65 were more likely to benefit from PCI than lesions with an FFR value of greater than 0.65 (p =0.01). This is presumed to be due to a greater ischaemic burden. Furthermore, it suggests that lesion location may not be the only variable that affects extent of ischaemia and this maybe one of the major limitations of jeopardy scores.

5.4.1. Clinical Implications

In principle, the f-BCIS score could be integrated into clinical standards due to its simplicity. However, a few areas of concern remain.

1.) The mean estimates of ischaemic burden by the f-APPROACH score (24%) and the f-BCIS (2.67 =23%) were twice the CMR estimate (11.2%). As such, 12% myocardial ischaemia by CMR (akin to 12% prognostically significant ischaemic threshold on SPECT) would be equivalent to a BCIS score of 3 or an APPROACH score of 26% (see figure 5.3).

2.) The specificity of a f-APP score >26% or a f-BCIS score of >3 is high and likely to be associated with a significant ischaemic burden supporting a decision to perform revascularisation. However the sensitivity for both these scores is modest, missing around a third of patients with significant ischaemia on the CMR scan. Further studies are therefore required to determine whether such a threshold has prognostic significance (see below) or how to further improve alignment of the two methods.

5.4.2 FUTURE DEVELOPMENTS

The estimation of ischaemic extent by CMR may be improved by fully quantitative perfusion analysis(20). There are currently novel developments to identify a perfusion threshold or absolute value for myocardial blood flow to allow a better estimation of ischaemic burden(4).

5.4.3 LIMITATIONS

One limitation of the study is using CMR as a reference standard when most of the data on ischaemic threshold is based on SPECT studies**.** We acknowledge that the 10-12.5% threshold for prognostically significant ischaemia may not apply to CMR but there is emerging evidence that the extent of ischaemia measured by the two modalities is similar (74). Another limitation is the consideration of the whole perfusion defect as the ischaemic area. This was done, as it can be difficult to accurately identify areas of peri-infarct ischaemia around scar. The number of patients with scar was small (n=3) therefore this is unlikely to have had an impact on the overall results.

5.5 CONCLUSION

The use of a functional jeopardy score integrates both anatomical and functional data from coronary angiography and FFR to provide an assessment of ischaemic burden. The functional jeopardy score can potentially be incorporated into interventional practice but further studies are required to see if this can be used to guide clinical decision-making.

CHAPTER 6. DIAGNOSTIC ACCURACY OF CMR IN MULTIVESSEL DISEASE.

6.1 INTRODUCTION

While there is a significant body of literature on the accuracy of both CMR and FFR for the detection of CAD, there are limited data on their comparability in defining ischaemic segments in patients with multi-vessel disease. Data comparing SPECT and FFR have shown fewer ischaemic territories with SPECT than FFR in patients with multi-vessel disease(143). It is well recognised, though, that the relatively low spatial resolution of SPECT may lead to underestimation of perfusion defects (89).

While most literature on non-invasive assessment of ischaemia is based on single photon emission computed tomography (SPECT), cardiovascular magnetic resonance (CMR) has shown advantages such as higher spatial resolution (3, 63) and potentially better diagnostic accuracy (5). It is unknown, however, whether the use of a high-resolution perfusion technique such as CMR leads to improved concordance for the identification of ischaemic segments in multi-vessel disease in comparison with FFR. The aim of this study was to compare the extent of myocardial ischaemia based on CMR and FFR in patients with angiographically defined multi-vessel disease.

6.2 METHODS

The local research ethics committee approved the study and all patients gave written informed consent to participate. A total of 41 patients with stable 2- or 3-vessel disease designated on a visual basis by angiography (diameter stenosis >50%) were recruited. Individuals who consented for the study had coronary angiography with FFR measurement and CMR scans within 4 weeks of recruitment.

Exclusion criteria were all contra-indications to CMR scanning (i.e. claustrophobia, metallic implant, pacemaker) contra-indications to adenosine therapy, previous coronary artery bypass graft (CABG), recent myocardial infarction (MI) within 6 months and left ventricular (LV) ejection fraction <30%.

6.2.1 CMR IMAGE ACQUISITION

Data were acquired with a 1.5T scanner (Achieva, Philips, Best, The Netherlands) using 32-channel coils. Examinations included high-resolution perfusion, cine and scar imaging. Perfusion imaging consisted of 3 short axis slices acquired every heartbeat covering 16 of the standard myocardial segments (apex excluded)(11) first during adenosine stress (140μg/kg/minute of adenosine administered intravenously for 3≤ minutes) followed by a short axis cine imaging stack and then rest imaging. Imaging parameters for perfusion imaging: kt-blast acceleration factor 5 SSFP sequence, shortest TE (range 1.35-1.54ms), shortest TR (range 2.64-3.12ms), 50° flip angle; 90° prepulse, 100ms prepulse delay and typical acquired resolution 1.7 x 1.9 x 10mm. A dual bolus(127) (equal volumes of 0.0075mmol/kg followed by 0.075mmol/kg after a 20 second pause) of weight adjusted contrast agent (Gadobutrol/Gadovist, Bayer Healthcare, Germany) was injected at 4ml/s by a power injector for stress and rest imaging. The cine images were completed with a set of long axis views. Late gadolinium enhancement (LGE) images were acquired after 10 minutes (Gadovist 0.2mmol/kg cumulative dose) using an inversion recovery sequence

6.2.2 CMR IMAGE ANALYSIS

CMR perfusion images were analysed by two experienced observers blinded to the angiographic data and clinical history (AC and SH). They reported all scans with consensus; any disagreement was arbitrated by a third reader (EN).

A perfusion defect was defined as reduced contrast uptake at peak stress persisting for 5 consecutive dynamic time points but not present at rest. Corresponding late gadolinium enhanced images were reviewed side by side with the perfusion data and enhanced myocardium was disregarded for ischaemia.

Designation of vascular territories was done according to AHA 17 segment classification(128). Segments 1, 2, 7, 8, 13, 14, and 17 were assigned to the left anterior descending coronary artery (LAD). Segments 3, 4, 9, 10, and 15 were assigned to the right coronary artery (RCA).

Segments 5, 6, 11, 12, and 16 were assigned to the left circumflex artery (CX). This analysis was performed without knowledge of angiographic variation as per clinical practice.

6.2.3 CORONARY ANGIOGRAPHY AND FFR MEASUREMENT

After obtaining either femoral or radial access, a standard Judkin's technique was used to obtain angiographic views. Multiple projections of the coronary arteries were acquired, including at least 2 orthogonal views to assess stenosis severity.

Pressure measurements were obtained in all vessels that showed a ≥40% diameter stenosis; lesser diameter stenoses were considered not significant. A 0.014-inch intracoronary pressure wire (Volcano Therapeutics, San Diego, CA, USA, or Pressure-Wire Certus, St Jude Medical Systems AB, Uppsala, Sweden) was inserted into the coronary artery. FFR was calculated during hyperaemia (intravenous adenosine infused at 140 micrograms kg/min for at least 90 seconds) as P_d/P_a, where P_d and P_a are distal coronary and aortic pressure respectively. In cases of serial stenoses or when there was diffuse disease, the pressure sensor was positioned beyond the most distal diseased segment and if the FFR was positive, this was ascribed to the most proximal lesion. A FFR of ≤0.75 was considered significant. Coronary occlusions or lesions of ≥99% were defined as FFR positive. Arteries with focal lesions < 40% diameter stenosis were defined as FFR negative.

6.2.4 ANGIOGRAPHIC ANALYSIS

Angiographic data was analysed offline at the end of the study. Coronary dominance was designated on the basis of the origin of the posterior descending artery. Quantitative assessment of coronary artery percent narrowing was performed with MDQM-QCA (Medcon Limited, Tel Aviv, Israel) software. Entirely smooth and occluded arteries were allocated 0% and 100% respectively.

6.2.5 STATISTICAL ANALYSIS

Data analysis was performed with SPSS version 20 (SPSS Inc., Chicago Illinois). Continuous variables were presented as mean ± standard deviation (SD). The k statistic values were derived to investigate per-patient and per-vessel concordance between FFR and CMR derived evidence for ischaemia (a k statistic of +1 indicating perfect agreement, 0 indicating agreement as expected by chance, and -1 indicating complete disagreement). In groups where kappa statistics could not be performed (i.e. where the value in one group was constant) concordance was assessed by percentage agreement.

Subgroup analyses according to arterial territories, FFR quartiles, single and multivessel disease were performed. Where possible the kappa statistic was used, otherwise percentage agreement was used and concordance was assessed.

The Mann Whitney U test was used to compare the mean number of ischaemic territories detected by CMR and FFR. Statistical tests were 2-tailed and $p<0.05$ were regarded as significant.

6.3 RESULTS

All 41 patients (29 males, average age 62±9 years) and 123 territories were included in the analysis. Table 6.1 summarises the clinical characteristics of the patients and the angiographic features. Table 6.2 summarises the CMR perfusion data. Two patients had subendocardial scar, none had transmural scarring.

Table 6.1: Pt clinical characteristics and angiographic details

Parameter	**Number or mean (+/- SD) (n=41)**
Age (years)	**62 (9)**
Sex (male) (n)	**30**
Height (m)	**1.71 (0.11)**

Weight (kg)		**81.0 (16.29)**
Body Mass Index		**27.8 (4.1)**
CAD risk factors (%)		
	Diabetes	**20.6**
	Hypertension	**60.0**
	Smoking	**14.3**
	Hypercholesterolaemia	**93.3**
Previous PCI (%)		**18.5**
Previous myocardial infarction (%)		**4.0**
Drug therapy (%)		
Aspirin		**81.5**
Statin		**80.0**
B blocker		**61.3**
ACE I		**29.6**
Angiographic details		
Vessels with FFR >0.75 (n)		**72**
Vessels with FFR ≤0.75 (n)		**51**
QCA in vessels with FFR >0.75 (% diameter stenosis)		**55.8 (18.1)**
QCA in vessels with FFR ≤0.75 (% diameter stenosis)		**81.3 (15.6)**

6.2: CMR Haemodynamic data

	Number or mean (+/- SD)
No of patients	41
Rest HR	63 (13.2)
Rest SBP	132 (21.3)
Rest RPP	8243
Stress HR	80 (18)
Stress SBP	129 (24)
Stress RPP	9889

Abbreviations: HR = heart rate, SBP= systolic blood pressure, RPP= rate pressure product

6.3.1 Comparison of CMR, FFR and QCA

CMR demonstrated no perfusion defect in 12 patients (29%), ischaemia in one territory in 20 (49%) patients, two territories in 8 patients (20%) and 3 territories in one patient (2%). All cases were read with consensus between two readers with only two cases requiring a third observer.

FFR results were negative in all vessels in 9 patients (22%), positive in 1 vessel in 16 patients (39%), in 2 vessels in 14 patients (34%) and 3 vessels in 2 patients (5%).

Using quantitative coronary angiography (QCA) with an angiographic cut-off of 50% defining significant stenosis results in the classification of 34 patients with 2- vessel disease (83%) and 7 patients with 3- vessel disease (17%). See figure 6.1.

Using quantitative coronary angiography (QCA) with an angiographic cut-off of 70% defining significant stenosis results in the classification of 7 Patients with 0 vessel disease (17%), 9 patients with 1- vessel disease (22%), 23 patients with 2- vessel disease (56%) and 3 patient with 3- vessel disease (7%). See figure 6.1.

The mean number of territories identified per patient was 1.0±0.8 by CMR and 1.2±0.9 by FFR.

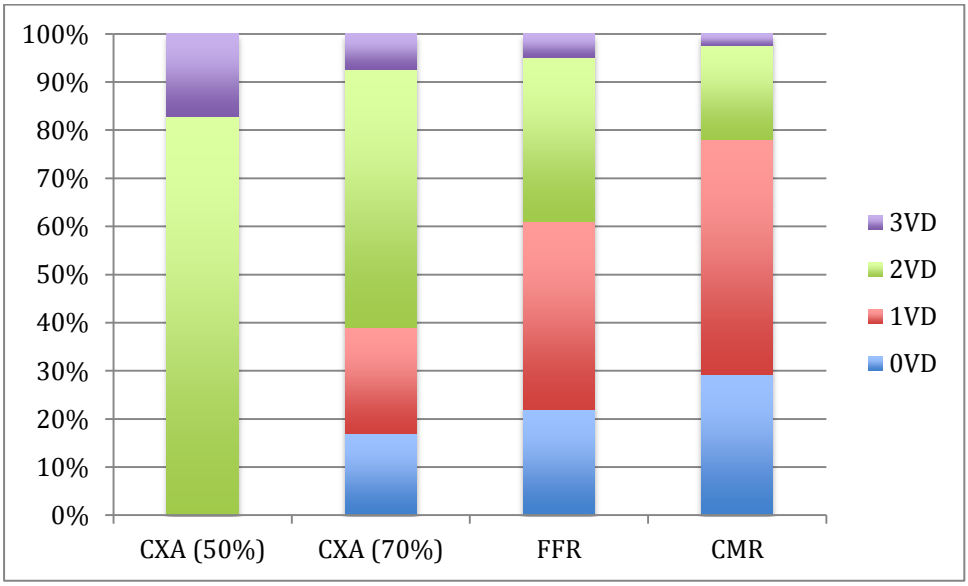


Figure 6.1: Respective proportion of number of vascular abnormalities as described by coronary angiography (based on a QCA cut off of 50% stenosis and 70% stenosis), CMR and FFR (CXA = coronary x-ray angiography)

6.3.2 Concordance between FFR and CMR

In 21 patients (51%), there was complete agreement as to the number of territories of ischaemia: mean no of territories 0.7±0.7 for both (p=1.0). Of these there was complete concordance in territories identified in 93 % of patients.

In 6 patients (15%), CMR showed more ischaemic territories than FFR, in 14 patients (34%),

CMR showed fewer ischaemic territories than FFR. See table 6.3.

The classification of 89 out of 143 territories (72%) was identical with CMR and FFR; of the discordant territories, in 20 (16%) CMR was negative and FFR positive and in 12 (10%) CMR was positive and FFR negative. See Fig 6.2 and Fig 6.3.

Overall, there was moderate concordance between the two methods on a per patient basis

(k =0.555: 95% CI 0.179-0.753) and on a per vessel basis (k=0.416: 95% CI 0.248-0.573). See table 6.4.

On a per patient basis, those with 0 or 1- vessel disease exhibited 72% agreement for the presence of any ischaemia, increasing to 88% in those patients with 2- or 3- vessel disease.

Table 6.3: Concordance between CMR and FFR on a per patient basis according to number of significant FFR values and CMR perfusion defects.

		FFR Result			
		0	1	2	3
CMR result	0	7	2	2	1
	1	1	11	8	0
	2	1	3	3	1
	3	0	0	1	0

.

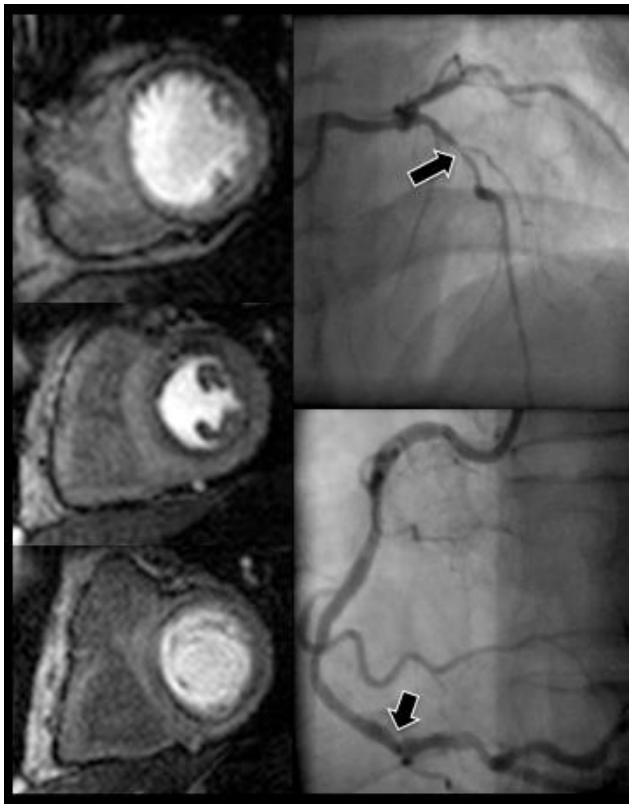


Figure 6.2: Case example of concordance between FFR value and CMR.

Angiographic images and corresponding perfusion images of a patient with 2-vessel disease. The LAD has a proximal stenosis (FFR value 0.63) (see arrow) resulting in a perfusion defect in the anterior wall visible in the apical, mid and basal ventricular slice.

The RCA has a distal stenosis (FFR value 0.62) (see arrow) resulting in a perfusion defect in the inferior wall visible in the basal and mid slice.

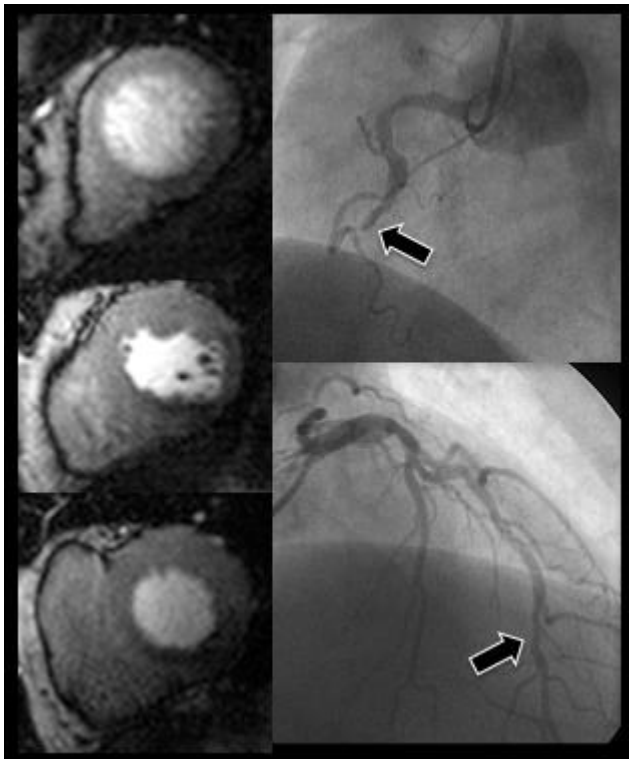


Fig 6.3. Case Example of discordance between the FFR value and CMR.

Angiographic images and corresponding perfusion images of a patient with 2-vessel disease. The LAD has a distal stenosis (FFR value 0.7) (arrow) with no associated perfusion defect.

The RCA has a proximally occluded artery (arrow) resulting in a perfusion defect in the inferior wall visible in all three slices. The combination of a distal lesion and a mildly positive FFR value results in no demonstrable ischaemia.

Table 6.4: Per vessel and per patient concordance between CMR and FFR

Concordance for the detection of ischaemia between CMR perfusion imaging and fractional flow reserve on a per vessel and a per patient basis.

CMR	FFR Result			
	Per vessel		*Per patient*	
	>0.75	**≤0.75**	**>0.75**	**≤0.75**
Negative	61	23	7	5
Positive	11	28	2	27

6.3.3 CONCORDANCE OF FFR QUARTILES AND VASCULAR TERRITORIES

Concordances between CMR and FFR for each territory: LAD artery concordance is poor: (k=0.159: 95% CI -0.104 – 0.423), CX artery concordance is moderate (k= 0.478: 95% CI 0.175 – 0.780), RCA artery concordance is also moderate (k=0.599: 95% CI 0.352 – 0.846).

Percentage agreement for each FFR quartile: 1st quartile 0-0.25 - 100% agreement; 2nd quartile 0.25-0.49 = 100 % agreement; 3rd quartile 0.5 – 0.75 = 44% agreement; 4th quartile 0.76 -1.0 = 84% agreement.

The lowest percentage agreement (42%) was found with FFR values of 0.7-0.8, of which the majority were in the LAD territory.

6.4 DISCUSSION

The data presented in this chapter shows reasonable concordance between CMR and FFR for the identification of myocardial ischaemia in patients with angiographic multi-vessel disease. On a per vessel basis, 89 out of 123 territories demonstrated concordance between the CMR and FFR results (72%). On a per patient basis there was complete concordance of number and localisation of territories in 46% of patients.

In one third of patients, CMR demonstrated a lower number of ischaemic territories than FFR. Agreement was best at the extremes of FFR (<0.5 and >0.75) but less strong for intermediate values. Concordance was best for RCA territory, followed by CX and worst for LAD.

6.4.1 FUNCTIONAL ASSESSMENT IN MULTIVESSEL DISEASE

Most previous studies specifically aimed at patients with multi-vessel disease have predominantly used SPECT as the non-invasive imaging test. In a study by Lima et al in 143 patients with proven angiographic 3–vessel CAD, myocardial perfusion imaging with SPECT demonstrated no significant perfusion defect or a single vessel pattern of disease in 54% of patients(88). This may be due to the lower sensitivity of SPECT, which has been attributed to its relatively low spatial resolution(89) or to the well-recognised disparity between angiographic and functional information (90). In the FAME cohort of patients, only 14% of the angiographically classified 3- vessel disease group had functional 3- vessel disease(91).

In a study by Melikian et al (143), the concordance between SPECT and FFR for the identification of ischaemic territories was poor (k=0.14 on a per patient and k=0.28 on a per vessel basis), which is interesting given that FFR was primarily validated against SPECT, albeit for the presence of ischaemia in single vessel disease (23). One of the limitations of this study was that 60% of the study cohort had either no or single vessel ischaemia when based on an FFR <0.8. Additionally, QCA measurement demonstrated an average stenosis severity of 50 - 60%. Thus the study probably reflects a low risk population rather than a true multi-vessel cohort. An earlier study by Ragosta (144) compared the concordance between FFR (using <0.75 as the cut-off for significance) and SPECT demonstrating agreement in 69% of cases. In

the majority of the discordant cases SPECT identified one stenosis and failed to identify a second or third stenosis regarded as significant by FFR. The reasons for the disparity of the two studies remains unclear and is unlikely to be solely due to the different FFR cut off values.

As mentioned earlier, the lower spatial resolution of SPECT may contribute to the lack of concordance. CMR perfusion imaging is an established imaging modality and the diagnostic accuracy of CMR has been assessed in multiple studies. A meta-analysis of 17, 901 patients showed an area under the curve (AUC) of 0.9055 for CMR (17), which was similar to PET and superior to SPECT imaging. In another meta-analysis, sensitivity, specificity and diagnostic accuracy were 0.91 and 0.81 respectively (18). Two recent studies have also shown results favourable for CMR. In the MR-IMPACT II trial, 533 patients underwent CXA, SPECT and CMR in 33 centres demonstrating a sensitivity of 75% which was superior to SPECT and a specificity of 59% which was inferior to SPECT (12). Additional subgroup analysis in multi-vessel disease, by different gender and in patients without prior MI also confirmed superior diagnostic accuracy. The CEMARC study, a larger (728 pts) single centre study showed a sensitivity of 86% for CMR which was significantly superior to that of SPECT at 66.5%, although specificity was similar (5). Subgroup analysis for multivessel disease in the CEMARC trial resulted in good diagnostic accuracy (AUC of 0.91 vs 0.77 for SPECT), however the assessment was on a per patient basis only and anatomic stenosis severity rather than FFR was used as the reference standard. A comparative accuracy study done by Chung et al(92) compared SPECT and perfusion CMR in patients with angiographically proven three vessel disease and showed that CMR detected perfusion defects in all three vascular territories in 57% of patients vs only 11% with SPECT.

6.4.2 THE "TRUE" GOLD STANDARD FUNCTIONAL TEST

Whilst trying to understand the causes of discrepancy between the two tests, it is worthwhile considering the applicability of FFR as a gold standard for ischaemia assessment. FFR is recognized to be a highly reproducible (26) and well-validated measure of ischaemia (23). The original validation, however, was against a number of non-invasive imaging modalities with a Bayesian statistical analysis involving a combination of all tests and demonstrating a

sensitivity of FFR in the identification of reversible ischaemia of 88% with a specificity of 100%. However, a meta- analysis of FFR vs QCA and non-invasive imaging by Christou et al demonstrated a sensitivity and specificity of 76% and 76% of FFR compared with non-invasive imaging (25). Compared to QCA, FFR had a sensitivity of 78% and a specificity of 51%. The differences between the different tests reflect the differences of the physiological measures used. Currently, none of the techniques can be regarded as the diagnostic reference standard.

CMR perfusion is also well validated against microspheres(7, 8), outcome (10, 11) as well as in large prospective studies (5, 12-14). In addition, recent work has focused on novel methods of quantitative perfusion analysis to improve diagnostic accuracy(4, 20).

As both investigations have extensive supportive data further work is required to define the "gold standard" for the assessment of myocardial ischaemia.

6.4.3 Discrepancy between CMR and FFR results

In this study, underestimation by CMR or overestimation by FFR is demonstrated in 33% of cases. This is similar to the two studies by Ragosta(144) and Melikian(143) discussed above.

For SPECT and PET, the concept of "balanced ischaemia" has been used to explain this underestimation, whereby some patients with 3- vessel disease often do not manifest perfusion abnormalities in all ischaemic territories or may have normal results due to globally reduced flow, which results in no focal perfusion defect (89).

There are a number of reasons why the concept of "balanced ischaemia" may not apply. Firstly, it is rare to have physiological 3- vessel disease based on FFR measurements. In the current study only two patients had 3- vessel disease based on FFR criteria. In the FAME study, it was found that only 14% of the anatomical multivessel population had functional multi-vessel disease (145). Secondly, the effect of physiological variables, i.e. length of vessel, length and severity of stenosis, area of myocardial bed, means that flow homogeneity in all territories is unlikely. Thirdly, the high spatial resolution of CMR means that the differences in flow between the three coronary territories and between the endo- and epicardium are more easily visualised (4).

Moreover, as alluded to by Ragosta et al(144), it is possible that the stenosis with the greatest ischaemia is more evident, leading to visual neglect of subtler perfusion abnormalities. In the majority of cases that were underestimated by CMR, the stenosis with the lowest FFR was identified correctly.

As mentioned earlier, concordance of results can also vary according to the FFR value used to define a flow-limiting lesion. A cut-off of 0.75was used in line with clinical practice, however as the greatest disagreement occurs at values of 0.7-0.8, it is likely that concordance would improve using a lower threshold of 0.7. Moreover, the lower concordance demonstrated in the LAD territory could be due to the high number of values within the 0.7-0.8 range in this territory (46%) compared to only 7% in the CX and RCA territories.

Any study that compares a non invasive with an invasive technique will be limited by the inability to define exact coronary territories by the 17 segment AHA model. Overlap of segments between the coronary arteries may lead to mis-assignment thus affecting concordance. Additionally in 2- vessel disease, depending on the functional severity of one stenosis compared with the other, it may be difficult to separate out two small areas of ischaemia from one larger more confluent area, again affecting concordance.

Furthermore, FFR may overestimate CAD. There are many physiological variables that can affect FFR measurement i.e. presence of scar, collaterals, FFR in small diameter vessels, microvascular dysfunction etc. and these are more likely to be present in patients that have extensive CAD such as our patient population.

While in general FFR is normalised for the perfusion area subtended by the interrogated vessel, a positive FFR in a small vessel may only lead to a small amount of myocardial ischaemia not detectable by CMR. Therefore, FFR may identify a greater amount of diseased vessels than ischaemic territories visualised on CMR.

In the data presented in this chapter, the prevalence of myocardial scar was low. However, the presence of scar does result in a perfusion defect, although the FFR should again be normalised to the smaller perfusion territory subtended by the vessel. Given that collateral contribution is also incorporated in FFR (as it is with CMR perfusion) this is also unlikely to be a source of discrepancy.

In a different population of patients, the presence of microvascular disease could result in positive CMR result in the presence of a negative FFR(80). Severe endothelial dysfunction can also result in myocardial defects on SPECT in some patients (e.g. diabetic) who have no significant epicardial stenosis(146).

6.4.4 Revascularisation in multivessel disease- clinical implications

CMR has practical advantages including its non-invasive nature, independency from ionizing radiation and applicability in all lesion subsets including chronic total occlusions (CTO's), calcified lesions, and severely tortuous lesions, in which FFR assessment is difficult.

6.5 Conclusion

This study shows that CMR demonstrates reasonable concordance with FFR for the identification of perfusion defects in multi-vessel disease. However, some discrepancies remain. There is a general tendency that CMR perfusion shows fewer diseased vessels than FFR. At this stage it is unclear whether CMR underestimates or FFR overestimates the number of ischaemic segments in multi-vessel disease.

6.6 Limitations

The main limitation of this study is the use of qualitative visual analysis. Quantitative or semi-quantitative perfusion analyses may further improve concordance and accuracy as recently shown in a study comparing visual and semi-quantitative CMR perfusion imaging versus invasive angiography in patients with known or suspected CAD (147). We have used visual analysis for the identification of perfusion defects as this is more applicable to clinical practice and our goal was the determination of similarities and differences between two clinically used tests.

Consistent with clinical practice, FFR was only measured in vessels in which there was a visual stenosis, which may lead to the unlikely situation of missing a positive FFR. Similarly, FFR was

not performed in >99% stenoses which may lead to vessels falsely assigned to the FFR positive group.

CHAPTER 7: NON INVASIVE DIAGNOSIS OF CORONARY MICROVASCULAR DYSFUNCTION

This chapter is written in combination with Dr Amedeo Chiribiri. It is part of a manuscript with the same title that has been submitted for consideration of publication.

I was involved throughout all major stages in the study including the trial design, patient screening and identification, data analysis and writing and final approval of the manuscript.

7.1 INTRODUCTION

Coronary microvascular disease (CMD) is diagnosed invasively by exclusion in patients with signs of myocardial ischaemia and angiographically normal coronary arteries (148). However, the non-invasive differentiation of CMD from epicardial CAD remains a diagnostic dilemma. Positron emission tomography (PET), SPECT, CMR and echocardiography provide useful information on the presence of myocardial ischaemia. This is not sufficient however to differentiate reliably between CMD and multi-vessel CAD including left main (LM) stem disease as all these conditions may be characterised by the presence of extensive myocardial ischaemia, which on visual and quantitative analysis can have a similar appearance (149). Consequently, patients are subjected to the risks of invasive angiography to identify or exclude the presence of epicardial CAD and their quality of life can be significantly impaired due to frequent hospitalisations for angina and repeated catheterisation (150).

Adenosine-stress first-pass perfusion CMR enables high spatial and temporal resolution perfusion data and has the potential to provide complementary information to visual and quantitative analysis for the study of coronary pathophysiology by the assessment of the spatio-temporal perfusion patterns(4, 151). Perfusion dephasing analysis is a novel strategy for the assessment of high spatio-temporal resolution CMR data that can provide new insights in the pathophysiological mechanisms underpinning the presence of myocardial ischaemia.

The aim of this study is to test whether perfusion dephasing analysis can provide elements for the differential diagnosis of multivessel CAD and CMD, and to compare it with visual and quantitative perfusion analysis.

7.2 METHODS

7.2.1 STUDY POPULATION

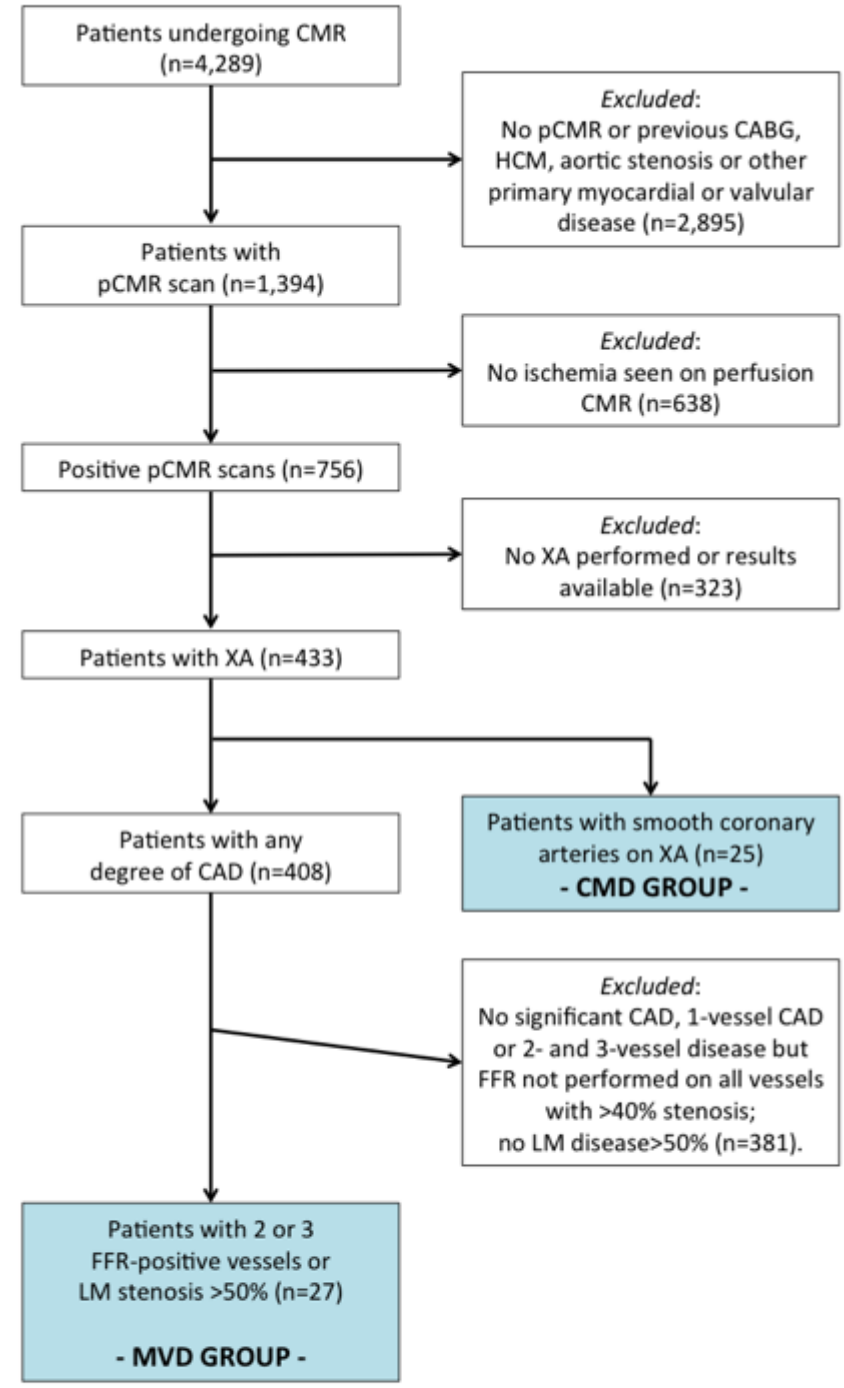
Patients were retrospectively screened from the registries of clinical CMR scans performed between March 2010 and December 2012 at the Department of Cardiovascular Imaging, King's College London and at the Cardiology Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, Portugal, accounting for 4,289 consecutive patients. Patients with previous coronary artery bypass grafting, hypertrophic cardiomyopathy, aortic stenosis or other primary myocardial or valvular disease were excluded. A total of 1,394 patients underwent CMR in the enrolment period (figure 7.1) and 756 were selected due to the presence of signs of ischaemia on CMR visual assessment. Results of invasive coronary angiography were available for 433 patients of these patients. Twenty-five had angiographically smooth coronary arteries and CMD was diagnosed by exclusion. These patients formed the CMD Group of the study.

The remaining 408 subjects were found to have some degree of CAD on angiography, ranging from minor lesions to three-vessel disease or LM disease. In the group of patients with angiographically 2- or 3-vessel CAD, 20 patients had a complete haemodynamic assessment of all lesions ≥50% stenosis with FFR and were found to have at least two vessels with haemodynamically relevant stenosis, indicated by FFR≤0.8. These patients, as well as 7 patients with ≥50% stenosis on the left main stem were enrolled to form the Multivessel CAD Group. Patients with incomplete functional assessment or patients with functional single-vessel disease were excluded from this group.

A control group including 12 healthy volunteers (Normal Group) recruited via university email was assessed by CMR using the same protocol used in patients. Exclusion criteria from this group were: known cardiac, respiratory, or renal disease or contraindications to CMR.

Moreover, a registry of 64 consecutive patients with known or suspected CAD referred for CMR in the inclusion period and who underwent invasive coronary angiography and FFR on all coronary stenoses ≥50% was also enrolled (CAD Registry Group). This group included patients with one haemodynamically significant coronary artery lesion, no haemodynamically significant lesions or only minor degrees of CAD. This study was performed in accordance with the standards set by the local ethics committee and all participants gave written informed consent.

STUDY GROUPS



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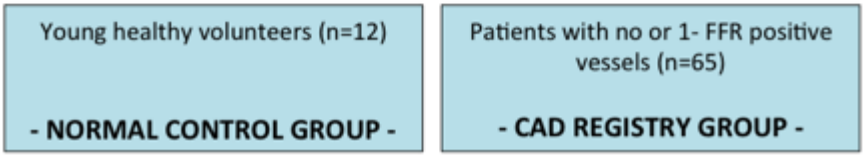

Fig 7.1: Study Flow diagram

7.2.3 CMR ACQUISITION.

CMR was performed at 1.5-T (Philips Intera, Philips Medical Systems, Netherlands or Siemens Avanto, Siemens, Germany) or 3.0-T (Philips Achieva-TX, Philips Medical Systems) using standard acquisition protocols (152). Examinations included adenosine stress and rest perfusion, functional and scar imaging.

Perfusion data were acquired in 3 left ventricular (LV) short-axis views covering 16 standard myocardial segments (153) during adenosine-induced hyperaemia over 3 minutes (140 μ g/kg/min) and 15 min later at rest using 0.075 mmol/kg gadobutrol (Gadovist, Schering, Berlin, Germany) at 4 ml/s followed by a 20-ml saline flush. A dual bolus protocol for contrast agent injection was used(119).

Perfusion imaging parameters at 1.5T: (Philips scanner): k-t blast acceleration factor 5, SSFP sequence, repetition time/echo time 3.1 ms/1.5 ms, flip angle 50°, 90° saturation pre-pulse, 100-ms pre-pulse delay, spatial resolution 1.7x1.9x10 mm^3; (Siemens scanner) gradient echo sequence (turbo fast low-angle shot), repetition time/echo time 1.5/0.99 ms, flip angle 12°, 90° saturation pre-pulse, 100-ms pre-pulse delay, spatial resolution 1.7x2.6x10 mm. Perfusion imaging parameters at 3T: *k-t* gradient echo method, repetition time/echo time 3.0 ms/1.0 ms, flip angle 15°, 90° saturation prepulse, 120-ms prepulse delay, spatial resolution 1.2x1.2x10 mm^3.

Functional data were acquired with steady state free precession cine sequences prescribed in short-axis and long-axis of the LV(152). Right and left ventricular volumes and function and LV mass were measured according to standard analysis criteria(154). Late gadolinium enhancement (LGE) images were acquired after 15 min after injection of a top up bolus of contrast agent performed after rest perfusion imaging to a total dose of gadolinium of 0.2 mEq/kg of body weight(152).

7.2.4 VISUAL CMR ANALYSIS.

Two blinded independent readers (NB, AS) visually assessed all CMR images. The scans

were judged positive for ischaemia in the presence of a stress-induced perfusion defect, defined as a delayed and reduced wash-in of contrast agent covering more than 60° circumferentially in the basal or mid slice or more than 90° circumferentially in the apical slice. In case of disagreement between the observers, the images were reviewed together, and a consensus was reached. Stress and rest scans and LGE images were viewed simultaneously, and areas of hypoperfusion were assigned to ventricular segments, using the standard 17-segment model, excluding the apex(153).

7.2.5 Quantitative perfusion analysis.

Quantitative analysis was performed by an expert blinded to all other clinical and invasive data. After automated respiratory motion correction and image segmentation(155), perfusion was quantified in 16 standard American Heart Association segments(153), excluding the apex, by using dedicated ViewForum software (Philips, Netherlands) and the Fermi deconvolution method(7). Each cardiac segment was assigned to the appropriate perfusion territory, with segment 15 assigned to the dominant coronary artery (defined by the observer analysing the angiogram). Myocardial perfusion reserve (MPR) was defined as stress perfusion estimate divided by rest perfusion estimate and was calculated for each segment and perfusion territory. The average MPR of the 2 lowest scoring segments for each perfusion territory was used for further analysis(63).

7.2.1 Perfusion dephasing analysis.

On visual analysis, abnormally perfused myocardium is apparent due to a reduced wash-in and the presence of transmural perfusion differences secondary to the increase of coronary resistance. (4, 151, 156) Both visual and quantitative perfusion analysis are based on the identification of abnormally reduced perfusion and cannot be used to differentiate multivessel CAD from CMD, as these both can be associated with extensive and diffusely abnormal perfusion patterns (149).

Different pathophysiological mechanisms however underpin the presence of ischaemia in patients with CAD and CMD. CAD is characterised by the presence of flow-limiting stenoses in one or more branches of the epicardial coronary arteries. CMD is caused by abnormalities in the function and structure of the coronary microcirculation(149). It is hypothesised that analysing the spatio-temporal distribution of contrast agent wash-in

across the LV wall could hold supplementary disease-specific information to visual and quantitative perfusion analysis, thereby allowing the differential diagnosis between multivessel CAD and CMD.

Perfusion dephasing analysis relies on the capability of CMR to acquire dynamic series of images with combined high temporal and spatial resolution, visualising the first-pass wash-in of contrast agent through the myocardium. It is hypothesised that the presence of haemodynamically significant multivessel CAD results in a temporally heterogeneous wash in of contrast agent in the myocardium due to the different localisation of the lesions in the coronary tree and the varied functional severity of the lesions. Conversely, CMD is characterised by an unobstructed epicardial flow in combination with a generalised intra-myocardial dysfunction resulting in a similar ischaemic burden but more homogeneous delay of the contrast agent wash-in across the LV myocardium (figure 7.2).

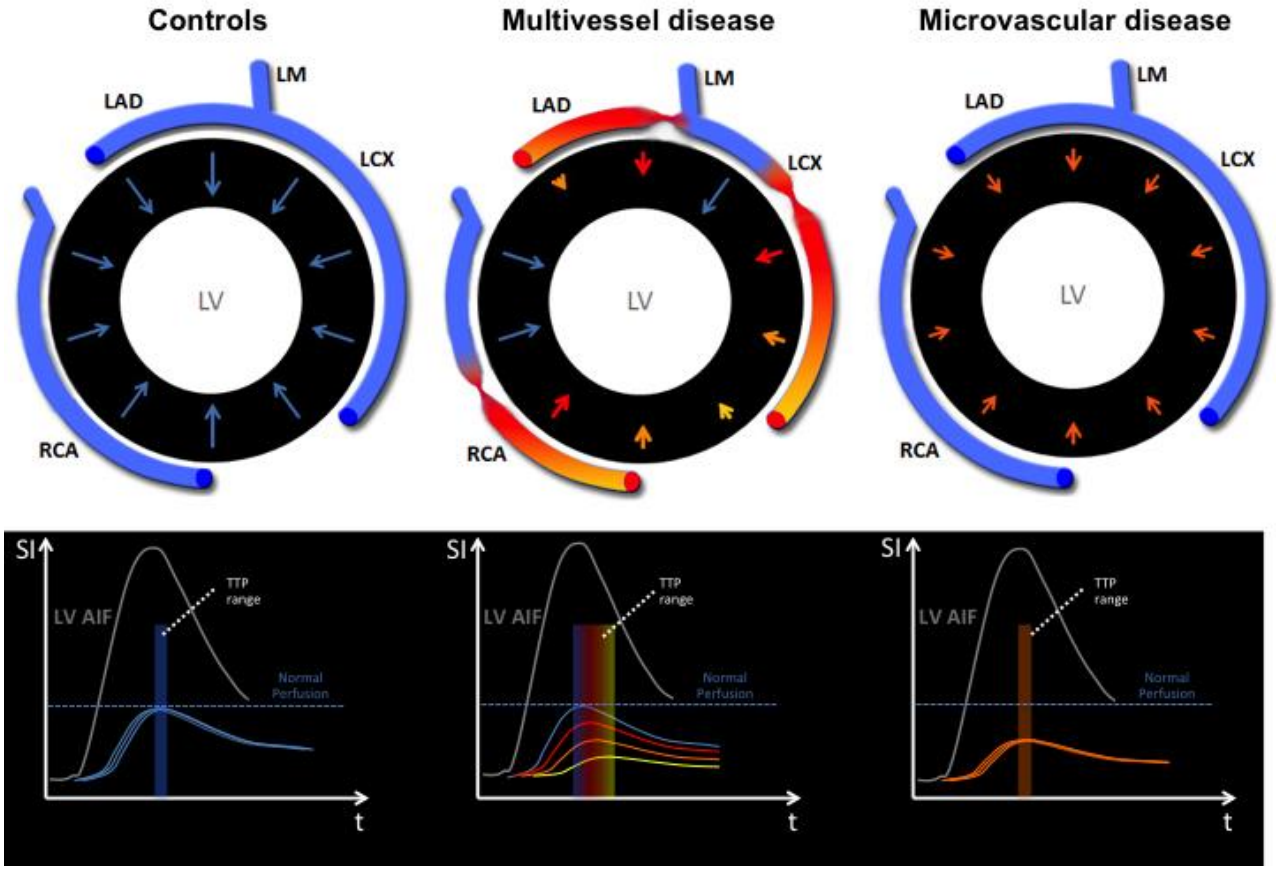

Figure 7.2: Pathophysiology of ischaemia in multivessel CAD and CMD.

Myocardial perfusion in a normal subject (left), in a patient with functionally significant three-vessel disease (centre) and in a patient with CMD (Upper row). The presence of haemodynamically significant multivessel CAD results in a temporally heterogeneous wash

in of contrast agent in the myocardium due to the varied localisation of the lesions and from the different severity of the stenoses. CMD is characterised by an unobstructed epicardial flow and by an intramyocardial delay of perfusion, evident with widespread subendocardial ischaemia but more homogeneous temporal distribution of the contrast agent across the left ventricular wall. (Lower row) In normal subjects, the upslope of myocardial signal intensity during first pass is relatively homogeneous in amplitude (normal perfusion dotted line) and temporal distribution (TTP range). In patients with multivessel CAD, myocardial perfusion is heterogeneous in absolute values and temporal distribution, whereas in patients with CMD myocardial perfusion is reduced in absolute values but homogeneous in the temporal direction.

Based on the same endo- and epicardial contours used for quantitative analysis a grid of 60 angular positions located on chords perpendicular to the myocardial centreline was generated(157). Transmural SI curves were then extracted for each angular position. To accommodate for the noise present in the perfusion CMR series, the extracted SI curves were filtered in both the spatial and temporal domain using a binomial filter. The temporal dephasing of LV perfusion was measured as variance or coefficient of variation of the time to peak myocardial signal intensity (TTP_{SI}). The variance of TTP_{SI} (VarTTP) is expressed in square seconds (s^2). The coefficient of variation of the TTP_{SI} is instead represented as a percentage. Both indices represent the temporal homogeneity of the TTP_{SI} across the LV myocardium.

Perfusion-dephasing analysis was performed by an observer blinded to clinical and invasive data using an in house programmed software (Labview, v2012SP1, National Instruments Corporation, TX, USA), relative to the onset of the main bolus arterial input function measured in the basal left ventricular slice. The analysis was repeated twice by the same operator and by a different blinded observer in order to measure the intra- and inter-observer variability.

7.2.2 STATISTICAL ANALYSIS

The Medcalc software (Medcalc, Belgium) and Analyse-it software (Analyse-it Software Limited, United Kingdom) were used. Data are presented as mean ± standard deviation. Shapiro-Wilk analysis defined when nonparametric tests were required. Intra- and inter observer reproducibility was determined by a coefficient of variation, defined as the ratio of the standard deviation of the differences divided by the mean, and by the Bland-Altman plot. Paired and independent t tests were used for comparison of paired and unpaired mean data, respectively. Receiver-operating characteristic (ROC) analysis determined the accuracy of visual and quantitative analysis in predicting the presence of multiple haemodynamically significant coronary artery stenoses and was used to compare these methods and perfusion-dephasing analysis for the differential diagnosis of multivessel CAD and CMD. Optimal cut-offs were determined by the best sum of sensitivity and specificity. ROC curves were compared using the De Long test. Because three coronary artery territories were examined on per-vessel analysis, the intra-class correlation coefficient was calculated to determine the design effect and the need to adjust the data for clustering.

7.3 RESULTS

A total of 129 subjects were included in the analysis groups. Baseline data and demographics for the enrolled population of patients and for each analysis subgroup are shown in table 7.1.

Table 7.1: Baseline characteristics of study participants

	All subjects (n=129)	**Multivessel CAD Group (n=27)**	**CMD Group (n=25)**	**Control Group (n=65)**	**Normal Group (n=12)**	**value**
Male Gender	90 (70%)	23 (85%)	15 (60%)	46 (71%)	5 (42%)	0.09
Age	57±13	62±8	58±9	61±9	28±6	<0.001
Hypertension	60 (47%)	15 (56%)	13 (52%)	32 (49%)	0 (0%)	0.008
Dyslipideamia	75 (58%)	21 (78%)	8 (32%)	46 (71%)	0 (0%)	<0.0001
Diabetes	20 (16%)	4 (15%)	4 (16%)	12 (18%)	0 (0%)	0.449
Current Smoker	19 (15%)	3 (11%)	0 (0%)	14 (22%)	2 (17%)	0.07
Previous MI	18 (14%)	7 (26%)	0 (0%)	11 (21%)	0 (0%)	0.248
Previous PCI	12 (9%)	2 (7%)	0 (0%)	10 (15%)	0 (0%)	0.08

Family history of CAD	33 (26%)	11 (41%)	2 (8%)	20 (31%)	2 (17%)	0.096
Body Surface Area (m^2)	1.9±0.2	1.8±0.2	1.9±0.3	2±0.2	1.7±0.3	0.005

Table 7.2: Angiographic details of population

	All patients (117 patients)	**Multivessel CAD Group (27 patients)**	**CMD Group (25 patients)**	**Control Group (65 patients)**
Per-vessel analysis				
Vessels FFR measured	107/351 (30%)	47/81 (58%)	0/75 (0%)	60/195 (31%)
Vessels FFR≤0.8	69/107 (65%)	45/47 (96%)	-	21/60 (37%)
Vessels FFR>0.8	38/107 (35%)	2/47 (4%)	-	39/60 (63%)
FFR positive vessels	0.6±0.14	0.61±0.14	-	0.57±0.13
FFR negative vessels	0.9±0.06	0.92±0.10	-	0.9±0.06
Vessels with FFR≤0.8				
LAD	35/107 (33%)	20/27 (74%)	-	13/60 (22%)
RCA	22/107 (21%)	16/27 (59%)	-	6/60 (10%)

LCX	12/107 (11%)	9/27 (33%)	-	2/60 (5%)
Per-patient analysis				
Vessels FFR measured	1.7±0.7	2.1±0.5	-	1.5±0.7
No significant CAD	69/117 (45%)	0/27 (0%)	25/25 (100%)	43/65 (66%)
1-vessel CAD	21/117 (17%)	0/27 (0%)	0 (0%)	21/65 (34%)
2-vessel CAD	17/117 (15%)	17/27 (63%)	0 (0%)	0/65 (0%)
3-vessel CAD	3/117 (3%)	3/27 (11%)	0 (0%)	0/65 (0%)
Left main stem ≥50%	7/117 (6%)	7/27 (26%)	0 (0%)	0/65 (0%)

Patients included in the CMD Group had normal epicardial coronary arteries by study design. Subjects in the Normal Group were not assessed by cardiac catheterisation.

7.3.1 CORONARY ANGIOGRAPHY AND FFR

Table 7.2 reports the angiographic and FFR findings. A total of 117 patients were evaluated with coronary angiography. Sixty-eight patients were judged not to have a significant CAD, 22 had functional single-vessel disease, 17 had functional two-vessel disease, 3 subjects had functional three-vessel disease and 7 patients had a ≥50% stenosis of the LM. A total of 107 vessels that showed a stenosis of ≥50% were assessed by FFR. Sixty-nine

lesions had FFR≤0.8 (median 0.62), 38 lesions had FFR>0.8 (median 0.89).

7.3.2 Perfusion CMR

Table 7.3 reports the functional CMR and LGE findings. The technical quality of the scans was thought to be adequate for diagnostic purposes on all subjects included in the analysis. Detailed results of visual assessment and quantitative perfusion analysis are shown in table 7.4 and table 7.5

Table 7.3: CMR findings

	All subjects (n=129)	**Multivessel CAD Group (n=27)**	**CMD Group (n=25)**	**Control Group (n=65)**	**Normal Group (n=12)**	**P-value**
LV EF (%)	78±15	65±7	65±8	59±9	61±6	0.333
LV EDV (ml/m^2)	31±11	71±16	74±8	77±14	92±13	0.260
LV ESV (ml/m^2)	75±16	25±8	26±7	32±12	36±8	0.187
LV mass (g/m^2)	60±17	69±21	72±26	54±11	58±9	<0.001
RV EF (%)	62±8	61±7	67±7	62±8	64±4	0.151
RV EDV (ml/m^2)	75±16	77±19	67±10	74±15	86±15	0.030
RV ESV (ml/m^2)	29±10	31±10	43±9	32±12	31±7	0.123
LA (cm^2)	23±5	23±3	25±5	23±5	19±2	0.006

RA (cm^2)	19±4	21±3	29±3	20±4	16±2	0.004
LGE +ve patients	19/129 (15%)	7/27 (26%)	0/25 (0%)	11/65 (17%)	0/12 (0%)	0.02
LGE +ve segments	0.5±1.3	0.8±1.7	0	0.6±1.3	0	0.046
Perfusion +ve patients (visual assessment)	70/129 (54%)	27/27 (100%)	25/25 (100%)	18/65 (28%)	0/12 (0%)	<0.0001
Perfusion +ve segments (visual assessment)	4.5±5 (28%)	8.4±4(53%)	10±4(63%)	1.2±2(8%)	0	<0.001

CAD – coronary artery disease; CMD – coronary microvascular disease; LBV- left ventricle; EF ejection fraction; EDV – end diastolic volume; ESV – end systolic volume; RV – right ventricle; LA – left atrium; RA – right atrium; LGE – late gadolinium enhancement ; RV – right ventricle; LA – left atrium; RA – right atrium; LGE – late gadolinium enhancement.

Table 7.4: Results of perfusion visual assessment in predicting functionally significant CAD (FFR≤0.8) in all subjects and after excluding patients with coronary microvascular disease.

ALL SUBJECTS											
	CAD (%)	**n**	**TP**	**TN**	**FP**	**FN**	**%Sensitivity (95%CI)**	**%Specificity (95%CI)**	**%PPV (95%CI)**	**%NPV (95%CI)**	**%Accuracy (95%CI)**
Per-vessel analysis											
All vessels	20	387	62	204	104	17	78 (68-87)	66 (61-71)	37(30-45)	92(88-95)	72 (67-78) se 0.027
LAD territory	30	129	28	63	27	11	72 (55-84)	70 (59-79)	51(37-64)	85(75-92)	71(62-79) se 0.044
RCA territory	17	129	20	69	38	2	91 (69-98)	64 (55-83)	34(23-48)	97(89-99)	78(70-85) se 0.039
LCX territory	14	129	14	72	39	4	78 (52-93)	65 (55-74)	26(16-41)	95(86-98)	?) se 0.055
Per-patient analysis											
	37	129	42	53	28	6	88 (74-95)	65(54-75)	60(48-71)	90(79-96)	76(69-84) se 0.036

EXCLUDING PATIENTS WITH CORONARY MICROVASCULAR DISEASE											
	CAD (%)	**n**	**TP**	**TN**	**FP**	**FN**	**%Sensitivity**	**%Specificity**	**%PPV**	**%NPV**	**%Accuracy**

							(95%CI)	**(95%CI)**	**(95%CI)**	**(95%CI)**	**(95%CI)**
Per-vessel analysis											
All vessels	25	312	62	204	29	17	78 (68-87)	88 (82-91)	68(57-77)	92(88-95)	83(78-88) se 0.026
LAD territory	38	104	28	63	2	11	72 (55-84)	97 (88-99)	93(76-99)	85(75-92)	84(77-92) se 0.038
RCA territory	21	104	20	69	13	2	91 (69-98)	84(74-91)	61(42-77)	97 (89-99)	88(80-95) se 0.037
LCX territory	17	104	14	72	14	4	78(52-93)	84(74-90)	50(31-69)	95 (86-98)	81(70-91) se 0.054
Per-patient analysis											
	46	104	42	53	3	6	88 (74-95)	95(84-99)	93(81-98)	90(79-96)	91(85-97)se 0.028

Table 7.5– Results of perfusion quantitative analysis in predicting functionally significant CAD (FFR≤0.8) in all subjects and after excluding patients with coronary microvascular disease.

ALL SUBJECTS											
	CAD (%)	**n**	**TP**	**TN**	**FP**	**FN**	**%Sensitivity (95%CI)**	**%Specificity (95%CI)**	**%PPV (95%CI)**	**%NPV (95%CI)**	**%Accuracy (95%CI)**
Per-vessel analysis											
All vessels	20	387	59	243	65	20	75% (63-84)	79(74-83)	48(39-57)	92(88-95)	82(77-86) se 0.024
LAD territory	30	129	28	67	23	11	72% (55-85)	74(64-83)	55(41-69)	86(76-92)	79(71-87) se 0.04
RCA territory	17	129	17	87	20	5	77(54-91)	81(72-88)	46(30-63)	95(87-98)	85(77-92) se 0.039
LCX territory	14	129	14	89	22	4	78(52-93)	80(71-87)	39(24-56)	96(89-99)	79(68-90) se 0.055
Per-patient analysis											
	37	129	40	53	28	8	83 (69-92)	65 (54-75)	59(46-70)	87(75-94)	75(66-83) se 0.044
EXCLUDING PATIENTS WITH CORONARY MICROVASCULAR DISEASE											

	CAD (%)	**n**	**TP**	**TN**	**FP**	**FN**	**%Sensitivity (95%CI)**	**%Specificity (95%CI)**	**%PPV (95%CI)**	**%NPV (95%CI)**	**%Accuracy (95%CI)**
Per-vessel analysis											
All vessels	25	312	60	218	15	19	76(65-85)	94(89-96)	80(69-88)	92(88-95)	91(88-95) se 0.019
LAD territory	38	104	28	61	4	11	72(55-84)	94(84-98)	88(70-96)	85(74-92)	93(87-98) se 0.026
RCA territory	21	104	17	80	2	5	77(54-91)	98(91-99)	89(65-98)	94(86-98)	93(87-99) se 0.029
LCX territory	17	104	14	77	9	4	78(52-93)	90(81-95)	61(39-80)	95(87-98)	86(76-97) se 0.052
Per-patient analysis											
	46	104	40	49	7	8	83(69-92)	88(75-94)	85(71-93)	86(74-93)	90(84-97) se 0.031

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7.3.3 Perfusion visual assessment

On visual assessment, areas of adenosine induced perfusion abnormalities were seen in 70 patients. According to the study design, all patients included in the Multivessel CAD and CMD groups were positive on visual assessment. Eighteen patients in the CAD Registry Group were positive. All subjects included in the Normal Control Group were negative to visual analysis.

Visual assessment allowed an accurate identification of the presence of functionally significant CAD defined by FFR (table 7.4). When all 129 enrolled subjects were analysed, the sensitivity, specificity and overall diagnostic accuracy were 78%, 66% and 72% on per-vessel analysis and 88%, 65% and 76% on per-patient analysis (table 7.4).

When patients with CMD were excluded from the analysis, the sensitivity, specificity and overall diagnostic accuracy of visual assessment were 78%, 88% and 83% (p=0.003) on per-vessel analysis and 88%, 95% and 91% (p=0.001) on per-patient analysis (n=104, table 7.4).

7.3.4 Quantitative perfusion assessment

Fermi-deconvolution quantitative perfusion analysis also allowed an accurate identification of the presence of functionally significant CAD (table 7.5). The average MPR in the perfusion territories classified as positive on invasive assessment was 1.3±0.5. In the remaining territories MPR was 2.1±0.8 (p<0.0001).

The sensitivity, specificity and diagnostic accuracy of quantitative perfusion analysis for the detection of haemodynamically significant CAD were 75%, 79% and 82%, respectively on per-vessel analysis and 83%, 65% and 75%, respectively on per-patient analysis (table 7.5).

When patients with diagnosis of CMD were excluded from the analysis, the sensitivity, specificity and overall diagnostic accuracy of quantitative assessment on the remaining 104 subjects were 76%, 94% and 91% (p=0.003), respectively on per-vessel analysis and 83%, 88% and 90% (p=0.005), respectively on per-patient analysis (table 7.5).

Quantitative perfusion assessment had similar diagnostic accuracy to visual perfusion assessment for the diagnosis of CAD on per-patient analysis (p=0.86), while it was significantly more accurate on per-vessel analysis (p=0.005). The same results were observed also after excluding patients of the CMD group from the analysis (p=0.81 and P=0.001, respectively).

7.3.5 Differential diagnosis of multivessel CAD and CMD

Visual assessment alone and quantitative analysis did not differentiate multivessel CAD from CMD (table 7.6). On average, the visual ischaemic burden was 0.5±1.3 positive segments per patient in the whole study population. This value was significantly higher in the Multivessel CAD Group (8.4±4 segments per patient; p<0.001) and in the CMD Group (10±4; p<0.001). However, no significant differences of the ischaemic burden were seen between the two latter groups (n=52; p=0.07).

On quantitative analysis, the 2 lowest scoring segments had an MPR of 1.1±0.4 in the multivessel CAD Group and 1.1±0.5 in patients in the CMD Group. The overall diagnostic accuracy of quantitative analysis in differentiating multivessel CAD from CMD was 61% (43-78%; p=0.09; table 7.6).

Table 7.6 – Differential diagnosis of coronary microvascular disease from multivessel CAD

	TP	TN	FP	FN	%Sensitivity (95%CI)	%Specificity (95%CI)	%PPV (95%CI)	%NPV (95%CI)	%Accuracy (95%CI)	P-value vs Visual	P-value vs Quantitative
					PATIENTS WITH 2/3 VISUALLY POSITIVE PERFUSION TERRITORIES (n=48; Multivessel CAD 43%)						
Visual analysis*	19	11	16	1	95(73-100)	41(23-61)	54 (37-51)	92(60-99)	53(36-70)	-	0.53
Quantitative analysis†	15	18	9	5	75(51-90)	67(46-83)	63 (41-80)	78 (56-92)	61(43-78)	0.53	-
Average TTP_{SI}‡	12	20	7	8	60 (36-80)	74 (53-88)	63(39-83)	71(52-85)	69(53-84)	0.18	0.51
Variance TTP_{SI}§	19	22	5	1	95(73-100)	81 (61-93)	79(57-92)	96(76-100)	89 (79-98)	0.0004	0.007
Coefficient of	20	25	2	0	100(80-100)	93 (74-99)	91(69-98)	100(83-100)	96(89-100)	<0.0001	0.0003

Variation TTP_{SI}#											

Best cut-off for CMD: * > 12 positive segments; † MPR<1.09; ‡ Average TTP_{SI}>13.9 s; § Variance TTP_{SI}<2.1s^2; # Coefficient of variation TTP_{SI} <10.

PERFUSION DEPHASING ANALYSIS

The detailed results of perfusion dephasing analysis are shown in figure 7.3 and table 7.6. The average value of TTP_{SI} increased in parallel with the extent of the ischaemic burden ($p<0.001$) and was significantly higher in patients with microvascular disease compared with all other groups ($p<0.001$ vs Normal Group; $p<0.001$ vs CAD Registry Group; $p=0.011$ vs Multivessel CAD group). TTP_{SI} was significantly higher in patients with Multivessel CAD compared with normals ($p=0.036$).

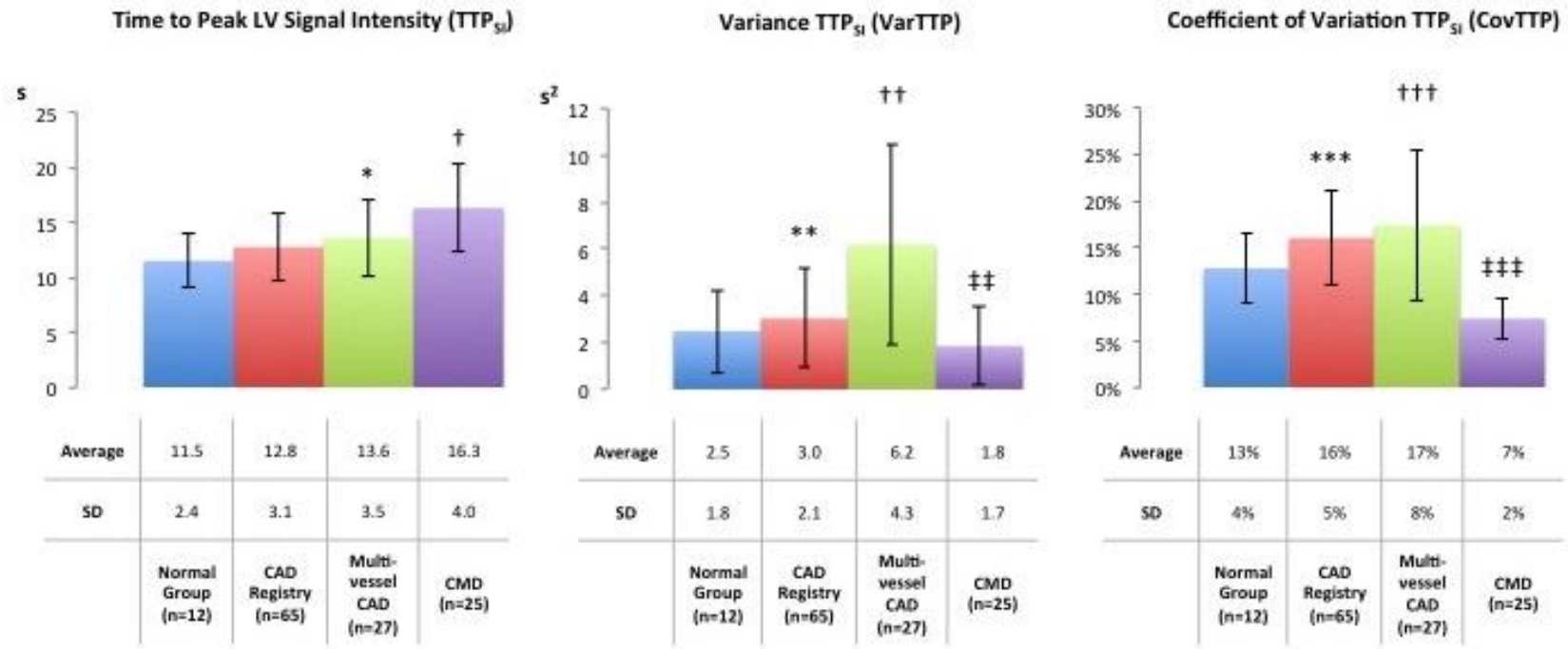

Figure 7.3 – Results of perfusion dephasing analysis.

* p=0.01 vs CMD Group and p=0.03 vs Normal Group; † p<0.001 vs Normal Group and CAD Registry Group; ** p<0.001 vs CMD Group and NormalGroup; p=0.004 vs CAD Registry Group; †† p=0.01 vs CAD Registry Group; *** p<0.001 vs CMD Group; p=0.01 vs Normal Group; ††† p<0.001 vs Normal Group and p=0.002 vs CAD Registry Group.

Perfusion-dephasing results correlated instead with the extent and severity of functionally significant CAD rather than directly with the ischaemic burden. Patients in the multivessel CAD Group had the highest perfusion dephasing ($VarTTP_{multivesselCAD}$ 6.2±4.3 s^2; $CovTTP_{multivesselCAD}$ 17%±8%) while patients with CMD showed very low perfusion dephasing, similar to normals ($VarTTP_{CMD}$ 1.8±1.7 s^2 vs $VarTTP_{Normals}$ 2.5±1.8 s^2; $p>0.05$) or even lower ($CovTTP_{CMD}$7%±2% vs $CovTTP_{Normals}$ 13%±4%; $p<0.001$) depending on the index chosen. There was a significant difference in VarTTP and CovTTP between the multivessel CAD and CMD groups ($p<0.001$ for both indices), which demonstrates the presence of a significant difference in the temporal homogeneity of the LV myocardial perfusion during adenosine stress despite the presence of a similar extent and severity of adenosine-induced ischaemia on visual and quantitative assessment.

The VarTTP was 89% accurate in the identification of multivessel CAD from CMD and has a significant added diagnostic value to both visual ($p=0.0004$) and quantitative analysis ($p=0.007$). The CovTTP was 96% accurate ($p<0.0001$ vs visual assessment and $p=0.0003$ vs quantitative analysis; table 7.6, figure 7.4).

The coefficient of variation of inter-observer variability was 50% for VarTTP and 14% for CovTTP. Intraobserver variability was 35% for VarTTP and 11% for CovTTP.**201**

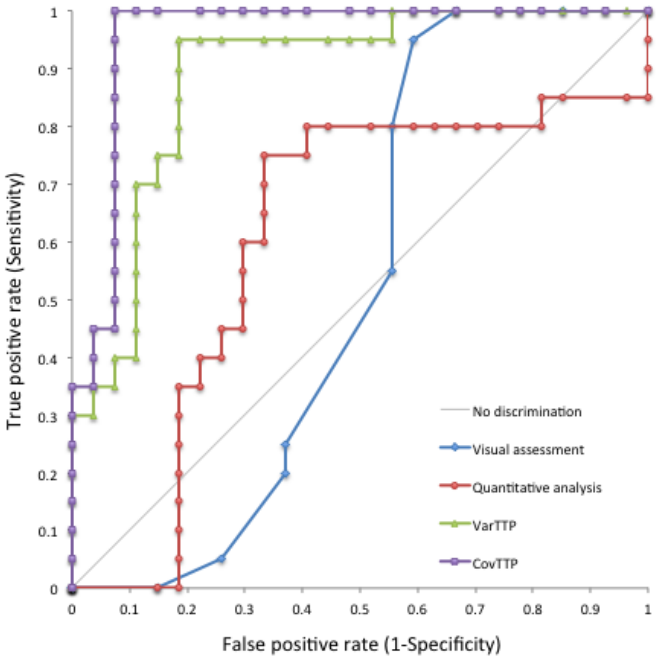

Figure 7.4: ROC curves comparing the diagnostic accuracy in differentiating multivessel CAD from CMD**.**

7.4 DISCUSSION

This study was designed to assess the novel concept of perfusion-dephasing analysis for the differential diagnosis of multivessel CAD and CMD and significantly adds to the current literature in several aspects.

1) Visual and quantitative assessment of CMR imaging allows an accurate diagnosis of functionally significant CAD as determined by FFR. Quantitative perfusion analysis is significantly superior to visual assessment for the detection of functionally significant CAD on a per-vessel analysis. The presence of patients with microvascular ischaemia however results in a number of false positive diagnoses against FFR, as ischaemia is found both in patients with CAD and with CMD. Visual and quantitative perfusion analysis cannot reliably differentiate between multivessel CAD and CMD.

2) Multivessel CAD and CMD can be accurately distinguished using non-invasive CMR based on the novel concept of perfusion dephasing analysis, which analyses the spatio-temporal variability in the distribution of myocardial perfusion to the LV myocardium.

Despite the well-defined link between CAD and myocardial ischaemia, a significant proportion of patients with angina are found to have normal epicardial coronary arteries. The non-invasive identification of these subjects is an important diagnostic dilemma, as CMD can present with signs of diffuse myocardial ischaemia similarly to multivessel CAD. The differential diagnosis therefore requires an anatomical assessment of the coronary arteries and CMD is usually diagnosed by exclusion (148, 149).

CMD is an important medical problem that remains difficult to diagnose and treat. Its prevalence varies amongst published studies, mainly as a result of differences in the definition of normal coronary arteries(158) and ranges between 20% in the CASS Registry(159)and 50% in the Women Ischaemia Syndrome Evaluation (WISE) Study(160) .

The prognostic significance of CMD is heavily debated. Data from the CASS Registry failed to demonstrate any prognostic implication of a positive ischaemic response in patients with normal coronary arteries (159), while in the WISE study the subgroup of women with chest pain and abnormal metabolism consistent with inducible myocardial ischaemia showed a significantly reduced event-free follow-up, similarly to patients with angiographic CAD(150). A systematic review including 1,694 patients with CMD from 16 different studies showed an incidence of a combined end-point of myocardial infarction, revascularisation and death of 1.5% at 5 years(161). There is however agreement in the literature on the deleterious effects of CMD on the quality of life of patients. The recurrence of angina is as high as 55% at 5 years and it usually results in repeated coronary catheterisation(161) .

The results of this study confirm that multivessel CAD and CMD are characterised by similar extent and severity of the LV ischaemia. This finding explains why non-invasive functional tests, based on the detection of the presence of ischaemia, cannot reliably differentiate

between groups. CMD however is thought to be one of the main factors responsible for the low diagnostic yield of coronary angiography (162) and the availability of novel tools for the non-invasive stratification of patients would clearly have the potential to significantly improve the management of patients.

Perfusion dephasing analysis is a novel technique of analysis complementary to visual or quantitative analysis and is based on a different and novel physiological principle, as it measures the spatio-temporal dephasing of LV wall perfusion rather than the presence of ischaemia. At the temporal resolution allowed by current CMR techniques (one frame/heart beat), normal myocardium has a relatively homogeneous perfusion, both in terms of absolute perfusion and temporal synchronisation. Functional multivessel CAD and CMD had a significantly larger ischaemic burden compared with patients with functional single-vessel disease, and in contrast to patients without significant CAD and normal volunteers, both on visual and quantitative assessment. This was reflected by the progressive increase of TTP_{SI} in parallel to the extent of the ischaemic burden. When the data were analysed in the temporal direction however, only patients with CAD showed an increase of the spatio-temporal dephasing of LV perfusion in parallel with the severity of the epicardial CAD. Patients with CMD, despite an even slightly higher ischaemic burden in comparison with patients with multivessel CAD, did not show any additional temporal heterogeneity of the TTP_{SI} across the LV wall in comparison with normal subjects.

This study has demonstrated that perfusion dephasing analysis adds diagnostic value to both visual and quantitative perfusion analysis. We therefore propose an improved diagnostic algorithm of CMR, including the analysis of the CovTTP, the most accurate index for perfusion dephasing according to our results, for patients with 2 or 3 perfusion territories positive for ischaemia (figure 7.5). A CovTTP>10.1% allowed in our population a reliable identification of multivessel CAD, importantly with 100% sensitivity and negative predictive value (NPV), ensuring that no patients with prognostically relevant multivessel CAD were missed, at the cost of 1 undue coronary catheterisation in a patient with normal coronaries. Moreover, one patient with functionally single-vessel CAD and visually judged as positive in 2 perfusion territories was also identified positive by the perfusion dephasing analysis and, although not

found to have functional multivessel CAD, the patient was correctly referred for coronary angiography.

Perfusion dephasing analysis has several additional advantages. The inherently better spatio-temporal resolution of CMR in comparison with other techniques makes perfusion dephasing possible regardless of the combination of CMR scanner, field strength and sequence. The algorithm is based on the detection of the TTPSI and not on its absolute value, making it very robust to signal dyshomogeneities as well as different data acquisition schemes. Moreover, perfusion dephasing does not require the administration of a dual bolus of contrast agent as performed in our patients to allow for MBF quantification.

7.5 CONCLUSION

In conclusion, perfusion dephasing analysis, a novel method to measure temporal differences of myocardial perfusion, is highly accurate in distinguishing patients with functionally significant multivessel CAD from patients with CMD and can easily be added to the current diagnostic protocol for perfusion CMR.

7.6 LIMITATIONS

This study included highly selected populations of patients with multivessel CAD or CMD. Perfusion-dephasing analysis will need to be tested on larger, multicentre and less selected populations of patients in the future, and the diagnostic criteria identified in this study independently validated.

The CAD registry group was enrolled retrospectively from the registry of CMR scans and FFR performed in the enrolment period. Since the indications for FFR were based on clinical grounds, a bias in this group towards a higher prevalence of intermediate lesions is likely.

Conflicting results on the presence of ischaemia in CMD patients are reported in the literature(80, 81, 83, 85). However, this study was not designed to address the dilemma of

the presence or absence of myocardial perfusion abnormalities in the subgroup of patients with coronary syndrome X, but solely to provide a tool to differentiate epicardial coronary artery disease and CMD in patients with a positive perfusion scan. The subjects enrolled in this study in the CMD Group were selected on the basis of positive CMR findings and showed a relatively high prevalence of coronary risk factors and LV mass and are thus more likely to represent a group of patients with CMD secondary to LVH. Similarly, patients with HCM were excluded to avoid the confounding effect of the variable geometry of the LV wall in the analysis of perfusion-dephasing data.

Perfusion-dephasing analysis is not suitable to assess microvascular impairment in cases of CMD secondary to obstructive CAD(149). However, these cases are likely to present with a degree of CMD directly dependent on the severity of the epicardial lesions and therefore following the spatio-temporal pattern of CAD. In these cases, perfusion-dephasing analysis would indicate the need for coronary angiography and missing these patients is therefore unlikely.

DIAGNOSTIC ALGORITHM

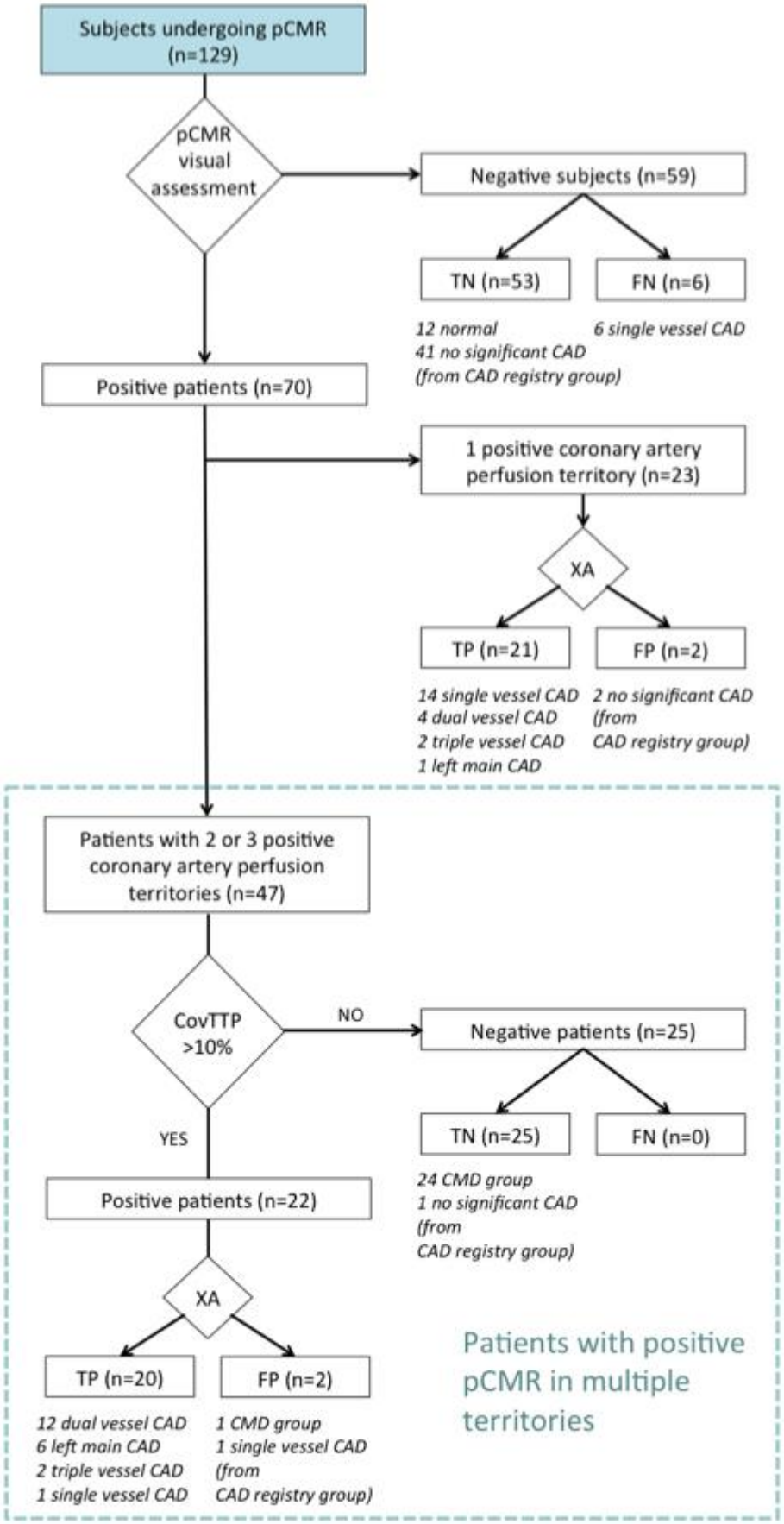

Figure 7.5: Revised diagnostic algorithm for the differential diagnosis of multivessel CAD and coronary microvascular dysfunction including the Coefficient of Variation of the Time to Peak Signal Intensity (CovTTP).

The best threshold of 10.1% identified from ROC analysis was used.

CHAPTER 8. SUMMARY

8.1 AIMS OF ORIGINAL WORK

This work was carried out with the main aim of enhancing our understanding of ischaemia assessment by CMR and FFR.

In particular, two areas of comparison between CMR and FFR have been assessed:

1) Investigating the relationship between the invasive assessment of stenosis severity and FFR measurement and ischaemic burden. This involves a novel development of the functional jeopardy score to provide a simple method of assessing ischaemic burden with FFR.

2) To investigate if there is a discrepancy in ischaemia assessment in multivessel disease. A novel CMR method to differentiate between multivessel disease and microvascular disease is developed and tested.

In this chapter, the extent to which these aims have been achieved, the limitations, the implications for the clinical management of these patients and future research in this area will be discussed.

8.2 MEASURES OF ISCHAEMIC BURDEN

As discussed in the introductory chapters, current guidelines stress the importance of physiological assessment of ischaemia for the guidance of revascularisation. There is particular research interest in the measurement of ischaemic burden and its reduction as a therapeutic goal.

This body of work contributes to the notion that the FFR value itself can be used as a marker of the extent of ischaemia. This work demonstrates a strong correlation between FFR values and the extent of ischaemia with the lower FFR values associated with greater ischaemia. The amount of ischaemia demonstrated by CMR reached a peak between FFR values of 0.5 – 0.4.

Furthermore, the lack of ischaemia demonstrated at FFR values >0.75 does lead one to question the benefit of revascularisation in the group with FFR values 0.75 – 0.8.

In particular, centres that do not have access to advanced imaging techniques such as CMR perfusion to guide revascularisation, could use the FFR value itself as an invasive marker indicating the extent of ischaemia. Findings from the landmark COURAGE trial have questioned the utility of PCI in patients with stable CAD. It is foreseeable, that in time, revascularisation guided by the FFR value itself may be related to prognostic benefit. If so, this could result in a shift in management with a reduction in unnecessary stenting procedures and the associated risks.

The limitations of modest numbers, especially in the values with very low FFR (<0.4) are acknowledged and it is difficult to know whether these values do actually represent a significant decline in ischaemic extent. The findings therefore need to be confirmed with larger scale studies and if established are potentially very exciting.

In chapter 5, the functional jeopardy score is described and it's potential to assess the extent of ischaemia invasively. There are limitations to this score that have been acknowledged, namely the significant overestimation when compared to the CMR assessment of ischaemia, and there is considerable variability in the estimation of CMR defined ischaemic burden. However, its correction by the severity of the FFR value in a weighted jeopardy score again lends importance to the FFR value itself as a major variable in the assessment of ischaemia.

One of the limitation's precluding the routine use of a jeopardy score is that it is an additional step in assessment during the procedure usually in busy catheterisation laboratories. More established scores such as the syntax score and the functional syntax score still remain in the realm of the research arena.
Although difficult to argue a true clinical value of the functional jeopardy score, the findings of both studies mentioned above do reinforce the concept of lesion location and FFR value as important markers of extensive ischaemia and lend weight to the strategy of revascularisation targeted to lesions causing the most ischaemia.

8.3 AREAS OF DISCREPANCY

Chapters 6 and 7 focused on the areas of discrepancy between the two tests. Although the high diagnostic accuracy of CMR has been confirmed in many studies, the accurate assessment of patients with multivessel disease is more problematic.

Chapter 7 highlights that although there is reasonable concordance, CMR does not correctly identify all ischaemic territories when compared to FFR. It is unclear whether this is related to underestimation by CMR, overestimation by FFR or a combination of both. The question then arises, of whether FFR is truly the gold standard especially as FFR was primarily validated against non-invasive imaging tests in patients with single vessel disease.

However, it is apparent from the data that the perfusion defects usually identified are those with the lowest FFR value. If, as we have ascertained, it is the lesion with the lowest FFR value that causes the most ischaemia then this throws the whole concept of multi-vessel revascularisation into the arena of debate. There is an argument, therefore, for reassessing a patient's symptoms and extent of ischaemia after targeted revascularisation to the lesion causing the most ischaemia.

At this stage, it is also important to mention the role of semi- and absolute quantification of myocardial perfusion. The CMR analysis used for chapters 4,5 and 6 was qualitative visual analysis. Full myocardial quantification was attempted, hence the use of the dual bolus method of contrast administration. However, the data was noisy and the quantification results did not correspond with the findings on visual analysis. It is difficult to know the exact reason for this but it is likely to be due to a combination of reasons. The dual bolus administration of contrast is complex and prone to errors. Additionally, with the small numbers of study patients, the presence of artefacts in even a small number of patients becomes more problematic. Furthermore the comparison with PET(20), the non-invasive reference standard had mixed results. Much of this is in contrast to visual analysis of perfusion, which is now a routine clinical tool. There are only a number of clinical situations where it is anticipated that quantification will be advantageous although to date data to support this are very limited.

In chapter 7, testing a novel quantitative method requires the comparison with more established quantitative measures i.e. Fermi deconvolution and thus the results are presented in this chapter.

Another diagnostic dilemma that is faced by the cardiologist interpreting multiple perfusion defects on a CMR scan is the differentiation between multi-vessel and microvascular disease. Currently there is no method of non-invasive differentiation of these two pathologies resulting in patients with microvascular disease being exposed unnecessarily to the risks of coronary angiography.

The novel concept of perfusion dephasing analysis, which analyses the spatio-temporal variability of myocardial perfusion to the LV myocardium, is introduced in chapter 7. The demonstration of reduced temporal homogeneity in patients with microvascular dysfunction compared to patients with multi-vessel disease could have a significant impact on management algorithms.

This method also appears to be more robust than absolute quantification as it is not limited by errors associated with the dual-bolus technique.

However, there are significant limitations to this retrospective data, with an obvious referral bias in those patients referred for catheterisation based on the standard CMR indices for perfusion. There is also a selection bias within the CAD group undergoing FFR evaluation as not all arteries are interrogated by FFR.

This concept is novel and therefore does require prospective outcome data in order to assess its clinical relevance. However, if its utility is proven, then it is foreseeable that dephasing analysis could potentially result in fewer diagnostic angiograms. At this stage, however, the majority of patients with a perfusion defect on CMR perfusion imaging would still be referred for coronary angiography.

8.4 AREAS OF FUTURE RESEARCH

The studies presented in this thesis raise some interesting questions, but firstly the results need to be confirmed with larger scale outcome studies.

As mentioned already, the incorporation of the functional jeopardy score in routine clinical practice is unlikely although there maybe a role in randomised clinical trials evaluating new therapeutic interventions with definition of the extent of the ischaemic burden as a normalising factor.

The use of the FFR value itself as an important variable in measuring the extent of ischaemia requires confirmation with larger scale studies. It could potentially be of great clinical relevance and may aid with decision-making regarding revascularisation in patients with multivessel disease, currently there appears to be no data available on which technique is best in describing ischaemia, and whether one tool over or under estimates the other in predicting the best strategy to guide revascularisation; therefore highlighting the importance of further research and larger clinical trials with long term follow-up. However, the low prevalence of patients with physiologically significant 3VD makes further research in this area challenging.

The major drawback of the dephasing study is that the data is retrospective and highly selected. The best test of this approach would therefore be a prospectively collected data set to determine which patients require invasive angiography and would truly test the diagnostic algorithm.

Some of the data used for the studies above is obtained from the MR-INFORM trial, which, once completed should provide extensive data to further explore the findings of this thesis. The MR-INFORM study however is not powered to test these specific end-points and so further outcome studies would be required to test the prognostic implications of some of the findings in this thesis.

No interim analysis is planned and so it is unclear what the final outcome will be. In the event of non-inferiority of CMR being demonstrated, CMR will be regarded as an equivalent to FFR for ischaemia testing without the inherent risks of an invasive procedure. Although establishing equivalence is the aim of the trial, this thesis emphasises the point that the type

of test used should be according to the clinical situation, and the real role for each modality is not in competition, but complementary to each other.

The results of the ISCHEMIA trial (https://www.ischemiatrial.org) are also eagerly awaited. This multinational comparative effectiveness trial aiming to recruit in excess of 8000 patients is currently recruiting. In this study, patients with moderate ischaemia on SPECT, stress echo or CMR (>12% ischaemia) will be randomised to either coronary angiography and subsequent revascularisation or optimal medical therapy. The primary objective of the trial is to see whether an invasive or conservative strategy leads to a reduction in the composite end-point of cardiovascular death or non-fatal myocardial infarction. This trial will again answer important questions on prognostic implications of revascularisation guided by extensive ischaemia.

8.5 Conclusion

In conclusion, the work in this thesis contributes to an enhanced understanding of the overlapping roles of two very different methods of ischaemia assessment.

FFR can be used to estimate ischaemic burden, traditionally the realm of the non-invasive imaging test, either directly via the use of the value itself or indirectly via the use of a functional jeopardy score.

CMR can be used to differentiate between microvascular and multivessel disease, previously only possible with invasive angiography.

The increasing use of CMR and the merging of boundaries between these tests can only be beneficial for patients provided that there is a good understanding of the differences and therefore appropriate referral.

Results from the on-going large multi-centre trials should further contribute to this area of research.

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PAPERS AND ABSTRACTS

PUBLICATIONS

Design and rationale of the MR-INFORM study: stress perfusion magnetic resonance imaging to guide the management of patients with stable coronary artery disease.
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ABSTRACTS

The correlation of FFR with ischaemic burden measured by CMR
Accepted for the European Society of Cardiology conference – Amsterdam 2013 ***(Poster presentation)***

Measurement of Ischaemic Burden: Validation of the functional BCIS score against CMR
Society of Cardiovascular Magnetic Resonance conference: 31 Jan -3 Feb 2013, San Francisco USA ***(Oral presentation)***

The design and rationale of the MR-INFORM study: CMR perfusion imaging to guide the management of patients of stable coronary artery disease
Society of Cardiovascular Magnetic Resonance conference: 1 – 4 Feb 2012, Orlando USA ***(Oral presentation)***

A comparison of single channel and multi-channel RF transmit coil for SSFP cine imaging at 3Tesla
Society of Cardiovascular Magnetic Resonance conference: 2 – 5 Feb 2012, Nice France. ***(Oral presentation)***

Utility of BNP testing within the primary health care setting. European Society of Cardiology "Heart Failure 2005" Conference – 11-14 June, Lisbon Portugal ***(Poster)***

LIST OF FIGURES AND TABLES